NOV 27 1939

Vol. 11 NOVEMBER, 1939 No. 1

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PUBLISHED BI-MONTHLY

OFFICIAL ORGAN OF
THE SOCIETY FOR THE STUDY OF ASTHMA AND ALLIED CONDITIONS
THE AMERICAN SOCIETY FOR THE STUDY OF ALLERGY

PUBLISHED BY THE C. V. MOSBY COMPANY, 3523 PINE BOULEVARD
ST. LOUIS, U. S. A.

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Vol. 11, No. 1, November, 1939. The Journal of Allergy is published Bi-monthly by The C. V. Mosby Company, 3523 Pine Blvd., St. Louis, Mo. Subscription Price: United States, its Possessions, Pan-American Countries, Canada, $7.50 a year; Foreign, $8.00. Entered as Second-Class Matter at Post Office at St. Louis, Mo., under Act of March 3, 1879. Printed in the U. S. A.

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The Journal of Allergy

VOL. 11 NOVEMBER, 1939 NO. 1

Original Articles

OBSERVATIONS ON TOTAL WATER AND SODIUM EXCHANGES IN ASTHMATIC PATIENTS*

JOHN SHELDON, M.D., HOMER HOWES, M.D., AND GEORGE STUART, M.D., ANN ARBOR, MICH.

IT HAS been agreed that one of the outstanding findings of allergic disease is local tissue swelling. It has been shown that the local swelling is associated with intracellular and extracellular edema. The sparsity of information in regard to the relationship of general body water and sodium to the local tissue edema has stimulated this investigation.

Five male patients, aged 14 to 51 years, were selected for study, because in each case an attack of asthma could be initiated or stopped as desired. They were all free from other complicating diseases.

The subjects were all placed on a weighed diet consisting of simple foods of known chemical composition. Their diet was approximately maintenance as to calories, and adequate in vitamins, minerals, protein, carbohydrate, and fat. During the entire period of study they were given the same foods in the same quantity for each of their three meals, except that in 3 persons an allergenic food was added to the diet to induce an asthmatic paroxysm.

The water intake was kept constant throughout the individual experiment but was varied in total amount in different experiments.

The salt intake was kept constant in each subject but was varied slightly in different subjects. The amount of the salt ingested by our patients was approximately equivalent to that taken by the average normal person.

Table I lists the quantity and types of foods, the amounts of protein, fat, carbohydrate, calories, potassium, and sodium chloride ingested over a twenty-four hour period by each subject. In Cases 1, 2, and 3 the diet was altered in order to produce asthma. The dietary change is detailed under the separate case reports.

*From the Department of Internal Medicine, University of Michigan.

Read at the Annual Meeting of the American Society for the Study of Allergy, St. Louis, Mo., May 15, 1939.

TABLE I

INTAKE OVER A TWENTY-FOUR HOUR PERIOD

SUBJECT	EXPERIMENT NUMBER	DIET					
		CARBOHYDRATE	PROTEIN	FAT	CALORIES	KCl	Nacl
		gm.	*gm.*	*gm.*		*gm.*	*gm.*
A. K.	1	493	53	53	2,657	3.85	11.1
C. A.	2	246	98	161	2,825	4.12	12.6
S. H.	3	332	40	32	1,776	3.87	14.4
H. S.	4	411	50	70	2,473	3.84	12.5
L. T.	5	189	99	131	2,366	3.51	6.5
R. R.	6	361	96	238	3,970	5.09	11.6

In each case study had proved the allergens to which the individuals were specifically sensitive. All the subjects were trained for a period of one week or longer in the technical procedures of water balance study. A control period of at least seven days was carried out to determine the heat elimination of each patient before starting the experimental period.

All urines were collected over a twenty-four hour period, thoroughly mixed and sodium determinations performed by the method outlined by Butler and Tuthill.[1] In some instances urinary chlorides[2] were determined as a check on the urinary sodiums. Insensible water was determined by the method of Newburgh.[3-5] The sodium chloride and potassium chloride contents of the diet were calculated according to tables of Bridges[6] and Sister Mary Victor.[7]

Each individual was placed on a constant diet with a fixed water intake for three days previous to the experimental period. At 8 A.M. of the fourth day the subject emptied his bladder, discarded the urine, and weighed himself, without clothing, on a beam balance, accurate to 1 gm. The dietary tray (of which the individual articles of the diet had been carefully weighed) was weighed on a scales accurate to 0.5 gm. The subject then ingested the food, and the empty tray was weighed. The noon and night trays were similarly checked before and after eating. Distilled water was weighed in a thermos jug each morning, and the subjects were permitted to drink from this container, as desired. They were, however, required to consume all of the water before evening. After the evening meal the weights of the food and water ingested were added together, and an additional quantity of distilled water was given to bring the total twenty-four hour intake to a constant level.

The urine, stools, nasal and bronchial secretions were collected in weighed porcelain buckets that had suitable tight lids.

At 8 A.M. of the second experimental day the subject voided into the urine container and again weighed himself. The urine, stools, and other secretions for the previous twenty-four hours were then weighed. From this data the insensible loss of weight was calculated.[3-5]

Determination of water intake was made by addition of the weights of food and drink. The water escaping from the subject was calculated by adding the weights of the stool, urine, and insensible water. If the weight of the fluid ingested was greater than the weight of the fluid excreted, the subject was considered to be in positive water balance. If the fluid eliminated from the subject was greater than the fluid of the diet and drink, the subject was considered to be in negative water balance.

Fractionation of the food, the stool, and the urine into water and solids was not done, because the total intake was maintained at a constant level. Any error that would arise by failure to determine the extra water fraction of the diet would be a constant, and, therefore, would not influence the results of any two periods of study.

Freyberg and Grant[8] have demonstrated that less than 0.5 gm. of sodium chloride is eliminated through the skin each twenty-four hours by insensible perspiration. A limited quantity of sodium chloride, usually under 1 gm., is excreted by way of the stool. Since the amount of sodium lost by these two pathways is relatively fixed and small in amount, no sodium determinations were performed on the stool or insensible water. Corrections may be made for these factors in estimating sodium balance.

CASE REPORTS

CASE 1.—A. K., an unemployed white male, aged 51 years, was first seen in the Medical Department of the University Hospital on Aug. 21, 1936, because of asthma. At the age of 39 he had had his first asthmatic attack, consisting of shortness of breath, wheezing, and cough. The paroxysms occurred at irregular intervals until December, 1934, when they became a daily occurrence. The attacks usually developed in the afternoon or early evening hours and showed no seasonal variation. By trial-and-error methods it was found that wheat, tomatoes, navy beans, and banana were the cause of his respiratory symptoms. By elimination of these foods he was symptom-free for three months previous to Oct. 4, 1938, his last admission date. There was no family history of allergic disturbance.

Physical examination: On the last admission physical examination revealed a white male of 51 years. The pulse rate was 78 per minute, the respiratory rate 18 per minute, and the blood pressure was 100/70 mm. His stature was average. The state of nutrition was good. The nasal mucous membrane was slightly hyperemic. The chest was emphysematous, but the expansion was free and equal. The lung fields were clear. The remainder of the examination was negative.

Laboratory examination: The Kahn test and urinalysis were negative. The sputum showed numerous organisms and many eosinophiles on direct (Wright) stained smear. Roentgenologic study of the nasal accessory sinuses showed slight thickening of the mucous membranes with moderate haziness of all paranasal sinuses. Stereoscopic roentgenograms of the chest showed bilateral basilar pleuritis with obliteration of the costophrenic sulci and mild pulmonary emphysema. Intracutaneous tests to protein allergens showed mildly positive reactions to wheat, feathers, and horse dander.

Experiment 1.—Subject A. K. (Case 1) was placed on a constant fluid, salt and dietary intake on Oct. 10, 1938 (Table I), and on Nov. 4, 1938, the water and sodium exchange study was begun. After a three-day control period 10 gm. of Pettijohn and 100 gm. of tomatoes were added to each meal. Ten grams of rice and 100 gm. of prune plum juice were simultaneously withdrawn from each meal. Eight hours after the addition of the allergenic foods, mild tightness in the chest was observed, and continuous asthma developed forty hours after the dietary change and persisted continuously for the next three days. The asthmatic attack promptly subsided after removing the Pettijohn and tomatoes.

Table II is a summary of the information obtained in Experiment 1. It will be observed that during the period of continuous asthma this patient lost 838 gm. of water and 2.7 gm. of sodium. It is also of interest that in the recovery period sodium and water were retained.

TABLE II

SALT AND WATER BALANCE OF SUBJECT A. K. (CASE 1)

DATE	BODY WEIGHT	FOOD AND WATER	URINE	STOOL AND SPUTUM	I.W.	WATER BALANCE	URINE Na/24 HR.	REMARKS
1938	*gm.*	*gm.*	*gm.*	*gm.*		*gm.*	*gm.*	
Nov. 4	56,477	4,500	3,199	185	1,421	-305	2.64	
5	56,172	4,500	2,872	124	1,484	+ 20	2.89	
6	56,192	4,500	3,072	91	1,269	+ 68	2.67	
7	56,260	4,500	3,129	94	1,277	0	2.71	
8	56,260	4,500	3,161	150	964	+225	3.09	Mild intermittent wheezing*
9	56,485	4,500	3,443	132	1,270	-305	3.77	Asthma
10	56,140	4,500	3,180	238	1,295	-213	4.32	Asthma, moderate
11	55,927	4,500	3,078	133	1,476	-180	2.71	Wheezing intermittent†
12	55,740	4,500	3,219	182	1,239	-140	2.41	Wheezing intermittent
13	55,600	4,500	3,053	70	1,277	+100	2.23	No chest findings
14	55,700	4,500	2,916	161	1,413	+ 10	2.34	
15	55,710	4,500	2,969	53	1,293	+185	2.17	
16	55,895	4,500	2,764	127	1,474	+135	2.15	
17	56,030	4,500						

*Ten grams of wheat and 100 gm. of tomatoes added to each meal.
†Wheat and tomatoes discontinued.

CASE 2.—C. A., an unemployed white male, aged 23 years, entered the University Hospital Feb. 3, 1939, because of asthma. Since infancy he had suffered from attacks of nasal obstruction, rhinorrhea, and pruritus of the eyes and nose. His first attack of asthma was at the age of 5 years, and was present in a greater or lesser degree since the onset. The paroxysms of dyspnea had no seasonal relationship. They would occur day or night and averaged two attacks per week. He had learned that sea food caused nausea, abdominal distress, "colds," and asthma. House dust, beer, and celery sometimes precipitated asthmatic attacks. Residence for several months in North Dakota and Washington failed to give him relief. His maternal grandmother had had asthma.

Physical examination: Physical examination revealed an adult white male. The pulse rate was 72 per minute, the respiratory rate 20 per minute, and the blood pressure was 114/70 mm. His stature was average. The nasal mucous membrane

TABLE III

SALT AND WATER BALANCE OF C. A. (CASE 2)

DATE	BODY WEIGHT	FOOD AND WATER	URINE	STOOL	BRONCHIAL SECRETIONS	BLOOD	I.W.	WATER BALANCE	URINE Na/24 HR.	cl/24 HR.	REMARKS
1939	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*c.c.*		*gm.*	*gm.*	*gm.*	
Mar. 28	61,426	3,300	1,524	207	0	6	1,621	- 58	4.57	7.15	
29	61,368	3,300	1,150	75	9	6	1,887	+173	4.49	5.69	
30	61,541	3,300	1,566	68	13	24	1,731	-102	4.63	9.95	
31	*61,439	3,300	1,435	253	47	55	1,818	-308	3.86	10.99	Asthma*
April 1	61,131	3,300	2,347	146	29	21	1,617	-915	5.90	9.67	Severe asthma
2	60,216	3,300	1,336	170	66	6	1,637	+ 85	3.96	6.42	Mild asthma
3	60,301	3,300	899	155	58	6	1,602	+ 85	3.47	5.39	Few wheezes
4	60,881	3,300	1,265	0	32	6	1,852	+580	4.93	6.98	Asthma free
5	61,026	3,300	1,370	279	36	6	1,709	+145	4.63	7.07	
6	60,926	3,300	1,456	84	15	6	1,839	-100	4.85	7.68	
7	60 826										

*One hundred grams of cooked salmon added to morning diet.

was pale and swollen, with a slight watery discharge in both nasal orifices. The chest was symmetrical and mildly emphysematous. The heart, abdomen, and extremities displayed no abnormalities.

Laboratory examination: The Kahn test and urinalysis were negative. Frontal stereoscopic roentgenograms of the chest were negative. Differential blood smears showed an eosinophilia of 5 per cent. Cutaneous skin tests were positive to milk, wheat, cotton seed, house dust, glue, salmon, perch, tuna fish, and whitefish. Intracutaneous tests showed additional positive reactions to feathers, lettuce, and potato.

Experiment 2.—Subject C. A. (Case 2) was placed on a constant fluid, salt, and dietary intake on March 8, 1939 (Table I). On March 28, 1939, the experimental period was started. After a three-day control period 100 gm. of salmon were added to his breakfast tray. At the same meal an isocaloric equivalent of beef and pork was taken from his diet. Within two hours after ingestion of the salmon marked asthma developed, which was constantly present for the next fifty-three hours. Mild wheezing after exercise or forced expiration was present until the morning of April 4, 1939.

Table III is a summary of the information obtained in Experiment 2. From this table it is observed that during the period of asthma there was a water loss of 1,223 gm. and approximately 1 gm. of sodium. During the period of recovery there was a retention of water and sodium.

CASE 3.—S. H., a white male, 24-year-old university student, was admitted to the University Hospital on Oct. 4, 1938, complaining of asthma. Since infancy he had had attacks of wheezing, inspiratory dyspnea, and cough, which occurred throughout the entire year but were worse in the spring, summer, and fall. By eliminating corn, spinach, peas, carrots, and cucumbers he had found that the winter asthmatic paroxysms were greatly reduced. He had been free from symptoms for three weeks previous to admission to the hospital. A brother suffers from late summer hay fever.

Physical examination: On admission physical examination revealed a young adult, undernourished, white male, having no obvious discomfort. The temperature was 98.4° F., the pulse rate 82 per minute, the respiratory rate 18 per minute, and the blood pressure 120/85 mm. There was a large scar over the upper left anterior chest wall. The posture was poor, accentuated by a marked upper dorsal kyphosis. The tonsils were large and cryptic. The chest was emphysematous. The lung fields were clear. The remainder of the physical examination was negative.

Laboratory examination: The Kahn test and urinalysis were negative. Frontal stereoscopic roentgenograms of the thorax showed an anomaly of the fourth left rib; otherwise they were negative. Differential blood smears revealed a 4 per cent eosinophilia. Cutaneous allergy tests were positive with *Alternaria* spores, wheat, egg, pea, feathers, cocoa, house dust, and orris root.

Experiment 3.—Subject S. H. (Case 3) was placed on a constant salt and dietary intake on Nov. 5, 1938 (Table I). On Nov. 13, 1938, the experimental period was started. Twenty-four hours later 200 gm. of spinach were added, and 200 gm. of beets were removed from each meal. Thirty minutes after the ingestion of the spinach, asthma developed and persisted for the next twenty-eight hours. The spinach

was stopped after three meals and replaced by beets. On Nov. 19, 1938, and again on Dec. 5 and Dec. 15, 1938, spinach was similarly given with resulting asthma, continuous for twenty-four to thirty hours.

From examination of Table IV it is apparent that in all instances when asthma was present there occurred a depletion of body water and a marked increase in the urinary sodium. On Dec. 5, 1938, this water loss consisted of 1,579 gm. An excess of 8 gm. of sodium chloride (3.2 gm. sodium) was excreted in the urine on this date. The excessive water and sodium chloride tissue loss may be directly attributed to the severe attack of asthma.

TABLE IV

SALT AND WATER BALANCE STUDIES IN S. H. (CASE 3)

DATE	BODY WEIGHT	FOOD AND WATER	URINE	STOOL AND SPUTUM	I.W.	WATER BALANCE	URINE Na/ 24 HR.	REMARKS
1938	*gm.*	*gm.*	*gm.*	*gm.*		*gm.*	*gm.*	
Nov. 13	53,163	2,797	1,488	48	1,364	-103	2.90	
14	53,060	2,800	1,645	265	1,474	-584	3.75	Asthma*
15	52,476	2,979	1,363	173	1,306	-180	1.71	
16	52,656	2,957	1,554	163	543	+745	1.04	
17	53,401	2,746	1,045	23	1,438	+241	2.34	
18	53,641	2,957	1,395	343	1,700	-481	2.12	
19	53,160	2,450	1,809	204	1,274	-737	4.85	Asthma*
20	52,323	2,058	466	60	1,315	+217	2.99	
21	52,540							
Dec. 3	52,920	3,037	1,436	132	1,204	+265	2.98	
4	53,185	3,000	1,399	170	1,284	+147	2.99	
5	53,332	3,000	2,712	396	1.471	-1579	6.22	Severe asthma*
6	51,753	3,000	1,347	161	1,532	- 40	4.06	
7	51,713	3,000	1,165	310	1,655	-200	3.25	
8	51,583	3,000	1,068	133	1,434	+365	2.79	
9	51,948							
Dec. 12	51,693	3,000	1,460	129	1,361	+ 50	3.28	
13	51,743	3,000	1,458	128	1,224	+190	3.41	
14	51,933	3,024	1,602	257	1,270	-105	3.34	
15	51,828	3,015	2,282	255	1,273	-795	4.65	Asthma*
16	51,033							

*Two hundred grams of spinach added to diet.

CASE 4.—H. S., a white male factory worker, aged 21 years, was first admitted to the University Hospital on Oct. 17, 1928, with the complaint of asthma. At the age of 4 years he developed eczema. Hay fever was first noticed at 6 years of age. Asthma developed the following year while in the middle of his hay fever season. Typhoid injections at age 8 relieved the eczema, but the asthma was only temporarily benefited. Following the hay fever season of 1934 the asthma became more or less persistent but occurred at irregular intervals. Thresher dust, house dust, peppermint candies, and peanuts were known causes of his asthma. A paternal uncle had had asthma, and a brother was a hay fever sufferer.

Physical examination: Physical examination on admission revealed a young, adequately nourished male in mild respiratory distress. The pulse rate was 104 per minute, the respiratory rate 28 per minute, and the blood pressure 104/78 mm. The conjunctivae were injected, and lacrimation was excessive. The nasal mucous membrane was pale and swollen. Excessive serous discharge was present in both nasal orifices. The chest was barrel-shaped with limited but bilaterally equal expansion.

Musical râles and rhonchi could be heard throughout the lung fields. The liver edge was palpable just below the right costal margin on inspiration. The remainder of the examination was of no diagnostic importance.

Laboratory examinations: The Kahn test and urinalysis were negative. Stereoscopic roentgenograms of the chest showed pulmonary emphysema. Differential blood smears showed an 8 per cent eosinophilia. Cutaneous skin tests for common allergens were positive for giant ragweed, dwarf ragweed, wheat rust, house dust, almonds, potatoes, corn, and celery.

Experiments 4 A and 4 B were carried out to determine if asthma associated with an inhalant allergen would produce the same changes in water and sodium balance as was found in the case of asthma due to food sensitization. The patient H. S. was placed on a constant salt, water, and dietary intake on Nov. 8, 1938. On Nov. 10, 1938, balance studies were begun, and after a control period of three days dwarf ragweed pollen in 60,000 pollen unit quantities was blown into the nose. A similar quantity of pollen was inhaled through the nose morning and evening for two days. Hay fever developed soon after the first exposure to the pollen, and asthma commenced within two hours. A continuous asthmatic paroxysm was maintained for three days. Table V is the summary of the data obtained in this experiment. It will be observed that 1,374 gm. of water and 4.5 gm. of sodium (7 gm. NaCl) were lost by the tissues of the subject during the three days of asthma.

TABLE V

(A) SALT AND WATER BALANCE STUDIES ON H. S. (CASE 4)

DATE	BODY WEIGHT	FOOD AND WATER	URINE	STOOL AND BRONCHIAL SECRETIONS	I.W.	WATER BALANCE	URINE Na/24 HR.	REMARKS
1938	*gm.*	*gm.*	*gm.*	*gm.*		*gm.*	*gm.*	
Nov. 10	54,095	4,000	2,183	131	1,830	-144		
11	53,951	4,000	2,122	117	1,602	+159	1.95	
12	54,110	4,000	2,268	159	1,513	+ 60	2.28	
13	54,170	4,000	2,543	259	1,462	-264	2.91	Hay fever and asthma*
14	53,906	4,000	2,491	602	1,662	-755	4.93	Severe asthma*
15	53,151	4,000	2,457	324	1,573	-355	2.71	Asthma
16	52,796	4,000	2,097	198	1,530	+175	2.49	Asthma free
17	52,971	4,000	2,176	269	1,304	+250	3.33	
18	53,221	4,000	2,611	265	1,123	0	2.55	
19	53,221	4,000	2,529	168	1,524	-221	2.74	
20	53,000	4,000	2,689	169	1,152	- 10	2.66	
21	52,990	4,000	2,465	97	1,378	+ 60	2.46	
22	53,050	4,000	2,608	168	1,289	- 65	2.24	
23	52,985	4,000						

*Dwarf ragweed pollen was blown into nose morning and evening.

In order to check the results of Experiment 4 A the experiment was repeated on Jan. 20, 1939, the results of which are detailed in Table VI. In this instance 2,013 gm. of water and 4.2 gm. of sodium (6 gm. NaCl) were lost during the three day period of asthma.

TABLE VI

(B) REPEAT OF SALT AND WATER BALANCE STUDIES ON H. S. (CASE 4)

DATE	BODY WEIGHT	FOOD AND WATER	URINE	STOOL AND SPUTUM	NASAL SECRETIONS	I.W.	WATER BALANCE	URINE Na/24 HR.	Cl/24 HR.	REMARKS
1939	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*		*gm.*	*gm.*	*gm.*	
Jan. 20	54,885	4,000	2,311	164		1,396	+229	1.82	3.28	
21	55,114	4,000	2,662	32		1,315	− 19	2.36	3.88	
22	55,105	4,000	2,505	75		1,306	+115	2.18	3.65	
23	55,220	4,000	2,515	142	2	1,786	−445	2.66	3.87	Asthma mild*
24	54,775	4,000	2,306	382	57	2,072	−998	4.00	5.77	Asthma severe*
25	53,777	4,000	2,403	347	38	1,782	−570	4.24	6.14	Asthma moderate*
26	53,207	4,000	1,749	425	39	1,692	+ 95	2.24	3.28	Asthma free
27	53,302	4,000	1,912	285	10	1,593	+200	1.31	1.82	
28	53,502	4,000	2,078	153	8	1,477	+284	1.30	1.95	
29	53,786	4,000	2,365	132	2	1,417	+ 83	1.82	2.99	
30	53,869	4,000	2,369	162	2	1,431	+ 36	1.87	3.00	
31	53,905	4,000	2,532	147	1	1,469	−149	2.16	4.77	
Feb. 1	53,756	4,000	2,366	120	2	1,551	− 40	2.72	4.16	
2	53,716		2,483	85		1,377	+ 55	2.45	3.76	
3	53,771									

*Dwarf ragweed pollen was blown into nose morning, noon, and night.

CASE 5.—L. T., a white male school boy, aged 14 years, was admitted to the University Hospital on Aug. 1, 1938, because of asthma. His first attack was at the age of 4 years. It continued to recur each fall, stopping with the first frost. From 1934 until the time of admission the attacks had been perennial with late summer exacerbation. It was thought that hay dust, house dust, and eggs would precipitate the paroxysms of asthma. His father and paternal uncle have had asthma.

Physical examination: Physical examination revealed an adequately nourished young male, of short stature, in a mild asthmatic attack. The pulse rate was 112 per minute, the respiratory rate 32 per minute, and the blood pressure 108/82 mm. The conjunctivae were injected. The nasal mucous membrane was tremendously swollen, completely occluding the left naris and partially obstructing the right nasal orifice. There was an audible respiratory wheeze. Sibilant and sonorous râles and rhonchi were heard throughout the lung fields. The heart was overactive but otherwise it was normal.

Laboratory examinations: The Kahn test and urinalysis were negative. Frontal stereoscopic roentgenograms of the chest were negative. The blood examination showed 95 per cent hemoglobin (Sahli), 12,100 W.B.C., and 8 per cent eosinophiles.

TABLE VII

STUDIES ON L. T. (CASE 5)

DATE	BODY WEIGHT	URINE NA/24 HR.	REMARKS
1938	*gm.*	*gm.*	
Aug. 12	35,543	2.68	Asthma moderate
13	35,636	1.89	Asthma mild
14	36,111	2.41	Asthma moderate
15	36,026	3.17	Asthma severe
16	35,941	2.84	Asthma moderate
17	35,756	2.05	Asthma moderate
18	36,125	2.78	Asthma moderate
19	36,291	2.93	Asthma moderate
20	35,945	2.90	Asthma moderate
21	35,650	2.14	Asthma very mild
22	34,534	1.81	No asthma
23	35,029	1.75	No asthma
24	35,335	1.54	No asthma

In order to determine whether inhalant asthma, spontaneously induced, would cause an alteration in sodium balance, subject L. T. was studied. He entered the hospital while having an asthmatic paroxysm. The experiment was continued until he had spontaneously recovered from this attack. Environmental allergens and pollen were, undoubtedly, the cause of his symptoms. The spontaneous recovery was, therefore, attributed to his removal from his environment and to a reduction in the ragweed pollen exposure. Water balance studies could not be carried out, since the hot weather precluded sensible perspiration. An analysis of Table VII reveals a marked reduction of urinary sodium when the asthma abated. The urinary sodium during the period of asthma was in excess of that expected with a constant intake of 6.5 gm. of sodium chloride daily (Table I, L. T.). Calculation of intake and output of sodium from the period of Aug. 12, 1938, through Aug. 21, 1938, reveals a total loss of 5.2 gm. of sodium (7 gm. NaCl).

Experiment 6 was performed in order to determine whether the results obtained in the pollen experiments were associated with the asthma, or whether they were due to the toxic or some other peculiar effect of pollen. A 24-year-old, nonatopic, medical student, was used as the experimental subject. He had been in good health with the exception of measles at age 6 years, and infrequent winter colds. The only abnormality in physical examination was mild obesity. He was placed on a constant salt, water, and dietary intake on April 10, 1938. Eight days later actual balance studies were begun and were continued for seven consecutive days. Pollen in 60,000 unit quantities was blown into his nose the morning and the evening of April 21, 23, and 24, 1939. A survey of Table VIII reveals no evidence of abnormal water elimination. The reduction in the urinary sodium excretion of April 20, 1939, is attributed to sweating.

DISCUSSION

Five patients in whom asthma could be initiated or stopped as desired were studied in regard to water and sodium metabolism. Three of the patients had their asthma initiated by foods; two by inhalant allergens.

The asthmatic attacks of our subjects were associated with a considerable loss of body water and a distinct elevation in urinary sodium. The sodium depletion was directly related to the body water loss, as measured by the balance studies. In many instances the urinary sodium during asthma was increased to twice the quantity eliminated during a comparable control period. The total twenty-four hour sodium excreted during the period of asthma reached a level of 3 gm. to 5 gm. more than was ingested. In the period of asthmatic recovery the urinary sodium was less than the amount of sodium ingested, but within a few days sodium excretion again returned to a preasthmatic level.

The water metabolism directly paralleled that of the sodium metabolism. The total loss of body water associated with an asthmatic attack in our subjects varied from 737 gm. to 2,013 gm. The increased urinary volume indicated that not all of the water was lost by increased lung ventilation. Furthermore, in the absence of disease an increased loss by one avenue was compensated by lessened loss through other channels. The phenomenon of water loss, in relationship to asthma, is not directly related to the fluid intake, since the latter was constant for any period, and different quantities of water ingested by the same subject during different experimental periods had no effect on water loss.

The loss of body fluid occurred in spite of a distinct edema of the shock organ. It would follow that a redistribution of fluid and electrolytes involving all tissues takes place; that in this redistribution

TABLE VIII

STUDIES ON A CONTROL INDIVIDUAL (R. R.)

DATE	BODY WEIGHT	FOOD AND WATER	URINE	STOOL	RESPIRATORY SECRETIONS	BLOOD	I. W.	WATER BALANCE	URINE NA/24 HR.	CL/24 HR.	REMARKS
1939	*gm.*	*gm.*	*gm.*	*gm.*	*gm.*	*c.c.*		*gm.*	*gm.*	*gm.*	
April 18	92,450	3800	1,685	170	0	0	2,167	−222	4.75	8.92	
19	92,228	3800	1,831	309	0	22	1,721	− 83	4.45	6.94	
20	92,145	3800	963	244	0	8	2,845	−260	3.56	7.58	
21	91,885	3800	1,866	44	0	18	1,872	0	5.46	8.59	Pollen* Sweating
22	91,885	3800	1,128	151	0	18	2,746	−243	5.37	8.74	
23	91,642	3800	1,123	225	0	6	2,518	−172	4.74	7.40	Pollen*
24	91,470	3800	1,173	111	0	6	2,280	+230	4.46	7.59	Pollen*
25	91,700										

*Dwarf ragweed pollen was blown into nose morning, afternoon, and evening.

there is a loss of water through the kidneys and an increased fluid content of the shock organ tissue.

It is impossible to measure accurately water and sodium exchange in asthma of short duration by the methods we have used, although alterations in water and sodium metabolism probably occur.

The total heat production was not greatly altered during an attack of asthma. Of 4 patients studied in severe attacks, in only one instance was the heat production elevated above that of experimental error. Hence, the increased loss of water that accompanies asthma cannot be attributed to extra vaporization of water that sometimes occurs when heat production is increased.

It is not the scope of this paper to include therapeutic applications of the study. Experiments in progress by us, and the work of Cook and Stoesser[10] would indicate a new approach to the management of allergic disease through an understanding of water and sodium metabolism.

CONCLUSIONS

1. A study of water and sodium metabolism has been carried out on 5 asthmatic patients.

2. There was a definite loss of body water associated with asthma of at least twenty-four hours' duration.

3. Urinary sodium was correspondingly increased during a prolonged asthmatic attack.

4. The total heat production during asthma was usually not measurably elevated; therefore, the loss in body weight that occurred was due to loss of body water.

The authors wish to express their sincere appreciation to Dr. L. H. Newburgh for the many helpful suggestions and careful guidance in preparation of this paper. We are indebted to Miss A. Beeuwkes for the dietary preparations.

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DISCUSSION ON "OBSERVATIONS ON TOTAL WATER AND SODIUM EXCHANGES IN ASTHMATIC PATIENTS," BY DRS. JOHN M. SHELDON, HOMER HOWES, AND GEORGE STUART; AND "ELECTROLYTE AND WATER EXCHANGES IN BRONCHIAL ASTHMA," BY DRS. A. V. STOESSER AND M. M. COOK*

DR. BEN. Z. RAPPAPORT, Chicago.—In discussing this subject with some of the physiologists at the University of Illinois, a similar conservative attitude was shown by those consulted. The work of Dr. W. F. Petersen, for instance, indicates that in patients with definite atopic conditions, as well as migraine, arthritis, and a number of other disturbances, a rapid and extensive change in the physiologic state will produce either marked improvement or exacerbation of symptoms. For instance, a change from the acid to a relatively alkaline state of the body fluids, and therefore of the tissues, produces marked changes in the permeability of the cells accompanied by changes in the concentration of the electrolytes of the cell. Such a change in the physiologic state of the individual will produce alteration in symptoms.

This is said in no way as criticism against the presentations. I have some confirmatory animal experiments to take up in the few minutes allotted by showing some slides lent to me by Dr. Walter Camp, of our Department of Pharmacology. These show the effect of potassium chloride compared with epinephrine intravenously in dogs.

(Slide) In this slide the effect of histamine on the bronchi is shown. Note that after the injection of potassium chloride the bronchi relax. One may see the similarity of the curves produced by epinephrine and potassium chloride. Both relax the bronchi following histamine injection. Dr. Camp informs me that sodium chloride, when injected previous to potassium chloride, will prevent such a reaction in all cases.

(Slide) In this case we have the intestinal constriction measured after the injection of 0.25 c.c. of 1:1,000 epinephrine solution. One may note the dilatation effect of this on the bowel. After this effect is over and the bowel is again in a normal state 1.5 c.c. of a 5 per cent potassium chloride solution is injected intravenously, a massive dose for a dog. The effect that may be noted is identical with epinephrine dilatation of the intestine. One may also observe the similarity of the blood pressure curves when the effect of epinephrine and potassium chloride is compared.

(Slide) This slide shows the auricular and ventricular contractions and the blood pressure curves following epinephrine and potassium chloride injections. The result of the injection of one is indistinguishable from the other.

No work has as yet been done on animals in the anaphylactic state. It is merely a comparison of the effect in the normal dog of potassium chloride and epinephrine.

To summarize, one must take into account the fact that in producing marked changes in the salt metabolism, as from the acid to the relatively alkaline side or vice versa, changes in symptoms are to be expected which are not necessarily specific effects. A patient whose course is toward improvement may improve markedly by such a rapid change in the permeability of his cells. If the same patient is in a downward phase, that is, if his condition is becoming worse, such a change may have no apparent effect or may even make him worse. From the experimental side the work has the merit of at least pre-

*See page 65 for abstract of this article.

liminary confirmatory evidence in dog experiments. These would indicate that with massive doses potassium chloride and epinephrine solutions produce similar effects.

DR. FRANCIS M. RACKEMANN, Boston.—We have heard two very important paper, both beautifully presented, and I congratulate the authors. I am not going to discuss the details of their observations, but there seems to be one or two points that might be called to our attention, chiefly because the observations here are analogous to one or two other clinical observations we may meet in our daily work.

Dr. Sheldon observed that there is a loss of water and salt in acute asthma, whereas in serum disease, you will remember, there was a retention of water and salt. In pneumonia there is a retention of water and salt, and we ought to try to correlate that in some way with this other thing. Perhaps Dr. Sheldon has some theory.

There is another interesting observation, namely, when a patient with asthma gets heart disease, a *cor pulmonale*, he will have edema, and it is my finding that as soon as edema appears, his asthma gets better. I do not know whether Dr. Sheldon will agree with that or not, but I have seen it several times and I have supposed, without knowing anything about it, that that change was concerned in some way with the modification of the water and salt metabolism.

Finally, there is one more point, and that is the effect of adrenalin, which is supposed to wash out sugar. I wonder if his patients with asthma had adrenalin, and whether this adrenalin might influence the physiologic changes which he observed.

DR. MILTON B. COHEN, Cleveland.—It seems to me that we have to be a little cautious about any application which we may make of any studies which are made of total water metabolism or total mineral metabolism, because by all of these methods we are measuring the end result of something.

When we do blood chemistry, for example, we are examining the river of the body, and we know nothing about what goes on at the docks. It is like looking at how many boats go down the Ohio River. That tells us nothing about how much business there is at Dock A, Dock B, or Dock C down on the levee. Dr. Sheldon, I think, very aptly pointed this out by saying that, while there is a total water loss in the attack of asthma, there is water retention in the shock organ, and a redistribution of fluid.

It seems we must await some methods which will enable us to study the tissues, and I am very glad to hear the second essayist tell us that he is now attempting some studies in the tissues themselves, where the business of life goes on.

One thing is very definite, at least to me, and that is that in allergic attacks there is a disturbance in mineral metabolism, not only of sodium and potassium, but also of calcium and other materials, often accompanied by definite change in the subcutaneous tissues, which can be seen in x-rays of soft tissue. While I am of the opinion that these are valuable additions to our knowledge, which point the way to future work, I want to emphasize that it is important that we study the tissues and do not draw conclusions on these total balance studies beyond those indicated.

I should like to ask Dr. Sheldon if he sees any objection to the conception of the tissues holding more fluid, perhaps outside even of the shock organ, in the presence of a reduction of total fluid in the individual.

DR. H. HAROLD GELFAND, New York.—I should like to ask Dr. Sheldon if he observed any alteration in urinary sodium or water metabolism immediately or for a time after a constitutional reaction from the injection of various allergens.

DR. ALBERT H. ROWE, Oakland, Calif.—These two contributions on water and electrolyte exchange deserve commendation, and the published articles will be worthy of our careful study. They confirm, of course, the clinical experience that definite attacks of asthma, especially when severe, are associated with dehydration. Therapy necessitates maintenance of water and electrolyte balance in all such patients.

In contrast to this dehydration in severe asthma, Dr. Rackemann has already recalled the water retention which occurs in serum sickness. Such retention with rather rapid increases in body weight has been recorded and observed by many allergists in other allergic patients, especially in those whose shock reactions occur in cutaneous and subcutaneous tissues. Generalized edema, evidencing itself in the outer tissues of the body, which undoubtedly extends throughout the whole organism, arises in occasional allergic patients. As the allergic attack subsides with desensitization or refractoriness, diuresis for hours or two or three days often occurs due to the release of water from the affected tissues. In this type of patient, therefore, water retention arises from uncontrolled allergy, in contrast to the dehydration in asthmatic patients studied in these two papers. Such water retention needs the careful clinical and laboratory study which has been given by the authors in these cases of severe asthma.

DR. ALEXANDER STERLING, Philadelphia.—I should like to ask Dr. Stoesser if the same result would be obtained with liquor potassium citrate.

Four or five years ago I noticed that children with very severe asthmatic attacks did very well when placed on liquor potassium citrate. With adults we used from a half ounce to an ounce four or five times daily. I attributed the good results obtained to the sedative effect of potassium citrate on the mucous membranes, as well as its expectorant properties. If the patient had a dry mucosa, with no râles, large doses of liquor potassium citrate increased expectoration, and in a few days the patient would feel very much better.

At that time I did not know this particular volume ratio and the chemistry of which you spoke. I wonder whether potassium citrate would have the same effect. If it does, it is a much more pleasant drug to take than potassium chloride.

DR. SHELDON.—I do not believe that Dr. Rappaport's discussion needs further comment.

Dr. Rackemann has raised questions in regard to serum disease, urticaria, and pneumonia which I am unable to answer. We have repeatedly observed persons with asthma who have obtained relief in the presence of pitting edema. It is my impression that such edema

of the extremities is associated with a mechanical factor due to the increased intrapulmonary pressure.

Dr. Rackemann asked about adrenalin. No adrenalin nor other drugs were given to any of the subjects during this study. The only alteration that was made in the patient's routine was administration of the allergen.

Dr. Cohen's comments are certainly in order. We wish to again stress the fact that this study is entirely an experimental approach we hoped would throw further light on some of the physiologic mechanisms of an allergic state. Dr. Cohen asked the question as to edema in one tissue and not in another. I am certain that such a phenomenon occurs. Some studies which we are carrying out would indicate that there is a rapid increase in blood volume immediately after the onset of an attack of asthma.

In answer to Dr. Gelfand's question, we have not performed short period determinations of sodium on any of our subjects; neither have we investigated water or sodium in other allergic conditions. We expect to carry out such studies in the future.

Dr. Cook.—We appreciate the suggestions and criticisms of the discussers, particularly the latter.

In reference to the work by Dr. Camp and Dr. Higgins, on the relationship between potassium and adrenalin, I may say that this may bear a fundamental relation to the work that we have reported. It suggests again the possible connection between electrolyte balance and neurogenic or endocrine functions.

The question about sodium citrate and acetate, I believe, I cannot answer. Perhaps we would better leave that to the clinicians. We use potassium chloride because potassium and chloride are strong base and acid, respectively, and the use of the citrate or acetate, or any other weaker ion would introduce other complicating factors. Also the chloride is a physiologic ion, one normally present in the body.

Dr. Cohen's point was well taken that the ultimate answer will be at hand when we investigate successfully the relationship between these factors in the cell and outside the cell and in the blood, in conjunction with the total water exchange.

I think that all of the discussers have reiterated that point and very properly so. Perhaps the answer to most of the questions that have been raised about these various procedures which have clinical value, may be at hand when we have the results of partitional metabolic experiments. They are very difficult to do, I might add, as any of you who have ever tried them will know, and the results have to be repeated and rechecked frequently so as to have a valid meaning.

THE THERMOLABILITY OF RAGWEED POLLEN EXTRACT AND ITS CORRESPONDING REAGIN*

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ALTHOUGH pollen extracts are known to deteriorate with age, their susceptibility to heat is still controversial. According to certain observers,[1-3] even autoclaving for ten minutes does not appreciably affect their reactivity in naturally sensitive individuals. On the other hand, Gay[4] and Long and Teller[5] have found that the activity of pollen extracts is definitely impaired after heating at 56° for one-half hour; and Stull, Cooke, and Chabot[6] found a marked loss in the activity of ragweed pollen extracts on heating for one hour in a boiling water bath. Similarly, Armstrong and Harrison[7] have demonstrated that heating an extract of short ragweed pollen at 65° C. for thirty minutes destroys its complement-fixing power with rabbit antisera.

These discrepancies may well be due to the inexact methods hitherto available for the assay of pollen extracts. In a recent communication[8] we have confirmed the fact that the method usually used—the determination of the highest reactive dilution of extract in naturally sensitive individuals—does not yield reproducible results, and often fails to detect even tenfold differences in activity. With a more reliable method of assay we have been able to confirm the thesis[4-7] that short ragweed pollen extracts are definitely thermolabile and lose 50 to 75 per cent of their reagin-neutralizing activity within fifteen minutes at 56° C.

In view of this pronounced thermolability the effect of the prolonged storage of pollen extracts at icebox temperatures was reinvestigated.[8-10] As will be shown, extracts of short ragweed pollen lost 75 per cent of their reagin-neutralizing activity within two years, and over 90 per cent in ten years. Furthermore, this progressive deterioration was apparently not accompanied by significant changes in the protein nitrogen content of the extracts.

One of the characteristics of atopic reagin is its relative thermolability as compared to other antibodies. Thus, Coca and Grove[11] found that reagin is appreciably inactivated by heating at 56° C. for one-half hour. This was confirmed by Gay and Chant.[12] However, no quantitative data have been presented as to the degree of inactivation and the time relationships involved. We have found that over 50 per cent of ragweed reagin is destroyed within thirty minutes at 56° C., and that it is almost completely inactivated after four hours at that temperature.

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Aided by a grant from Hynson, Westcott, and Dunning, Baltimore.

METHODS

1. *Assay of Pollen Extracts.*—The method used for assaying the heated extracts is based on their relative reagin-neutralizing activity in vitro. It is essentially the same as that used by Cooke and his coworkers,[13] and has been described in detail in a recent paper.[14] Briefly, serial twofold dilutions of each* of the ragweed pollen extracts to be tested are first prepared. To 0.2 c.c. of each dilution is then added 0.2 c.c. of a reagin-containing serum from a ragweed sensitive individual. Each set of mixtures, usually consisting of eight tubes, thus contains a fixed amount of the same serum and varying amounts of some one of the extracts.

The mixtures are shaken and placed at 37° C. for one hour. One-twentieth to 0.1 c.c. of each mixture is then injected intradermally into normal recipients in a vertical row on the volar aspect of the upper arm and forearm.† Four such parallel rows, representing four different extracts can be injected without crowding into one recipient, two on each arm. At least two recipients are used for each set of four extracts. Twenty-four to forty-eight hours later each of the sites is tested by the intradermal injection of approximately 0.01 c.c. of a 1:100 dilution of the unheated ragweed extract. The size of the skin reaction after twenty minutes is then noted. The amount of each extract which just suffices to prevent passive sensitization, as evidenced by the negative skin reaction on retesting, is taken as its neutralizing concentration. The neutralizing concentration of a standard, unheated extract (e.g., 1:100), divided by the neutralizing concentration of some heated extract *in the same recipient* (e.g., 1:20), is a measure of the relative activity of the latter (e.g., $\frac{1}{5}$). It is apparent that the more recipients used for each such comparison, the smaller will be the experimental error of the average.

2. *Assay of Atopic Ragweed Reagin.*—The method of assaying the reagin content of the sera was essentially that used by Coca and Grove,[11] and consisted in the determination of the highest dilution of serum which would passively sensitize the skin of a normal individual.

Serial twofold dilutions of the sera to be tested are first prepared, usually ranging between 1:5 and 1:640. Approximately 0.05 to 0.10 c.c. of each dilution is injected intradermally into the volar surface of the upper arm and forearm, the eight dilutions forming a vertical row extending from the shoulder to the wrist. Four such rows, two on each arm, can be injected without crowding into one recipient. At least two recipients are used for each set of four sera. Twenty-four to forty-eight hours later each of these sites is tested with approximately 0.01

*Three different portions of the extract, heated at 56° C. for varying periods of time, were compared to the unheated extract in each experiment.

†The recipient should be a known receptor and should not be skin-sensitive to ragweed extract.

TABLE I

EFFECT OF HEAT ON THE REAGIN-NEUTRALIZING ACTIVITY OF A SHORT RAGWEED POLLEN EXTRACT

DILUTION OF EXTRACT ADDED TO EQUAL VOLUME OF SERUM W. S.	RECIPIENT 361				RECIPIENT 362			
	SERUM W. S. NEUTRALIZED PRIOR TO INJECTION WITH							
	UNHEATED EXTRACT	EXTRACT HEATED AT 56° C. FOR			UNHEATED EXTRACT	EXTRACT HEATED AT 56° C. FOR		
		½ HOUR	1 HOUR	2 HOURS		½ HOUR	1 HOUR	2 HOURS
	SIZE OF REACTIONS* OBTAINED ON RETESTING PASSIVELY SENSITIZED SITES 24 HOURS LATER WITH 1:100 UNHEATED EXTRACT							
Conc.		0	0	0		0	0	0
1:2		0	0	±		0	0	0
1:5		0	±	4-15		0	0	±
1:10	0	±	5-25	5-20	0	0	3-10	5-20
1:20	0	6-20	5-25	7-25	0	5-20	3-10	6-25
1:40	±	7-25	7-25	10-30	0	6-25	5-20	7-25
1:80	5-20	8-30	10-30	10-30	3-10	7-25	6-25	7-25
1:160	6-25	10-30	10-30	10-30	6-25	8-30	7-25	7-25
1:320	7-30				7-30			
1:640	7-35				8-30			
1:1,280	8-30				8-30			
0 (NaCl control)	8-30				8-30			
Minimal concentration of extract necessary to neutralize serum reagin	1:30	1:7.5†	1:3.5†	1:1.5†	1:40	1:10	1:5	1:3.5†
Relative activity of the four extracts, referred to unheated extract as 100	100	25	12	5	100	25	12	9

*In the body of the table, the first number refers to the average diameter of the wheal in millimeters, and the second number indicates the average diameter of wheal plus erythema.

†Arbitrarily interpolated between the concentration of extract which completely neutralizes, and that which just fails to neutralize, the serum reagin.

c.c. of a 1:100 dilution of stock short ragweed extract. The skin reactions are read in twenty minutes. The highest dilution of serum which just suffices to sensitize the skin is taken as the measure of the reagin content of the serum.*

EXPERIMENTAL

Thermolability of Short Ragweed Pollen Extracts at 56° C.—A typical experiment illustrating the effect of heating at 56° C. on the activity of short ragweed pollen extracts is given in Table I. As is there shown, in recipient 361 a 1:30 dilution of unheated ragweed extract sufficed to neutralize the particular serum used; when whole extract was heated at 56° C. for one-half hour, a 1:7.5 dilution was necessary

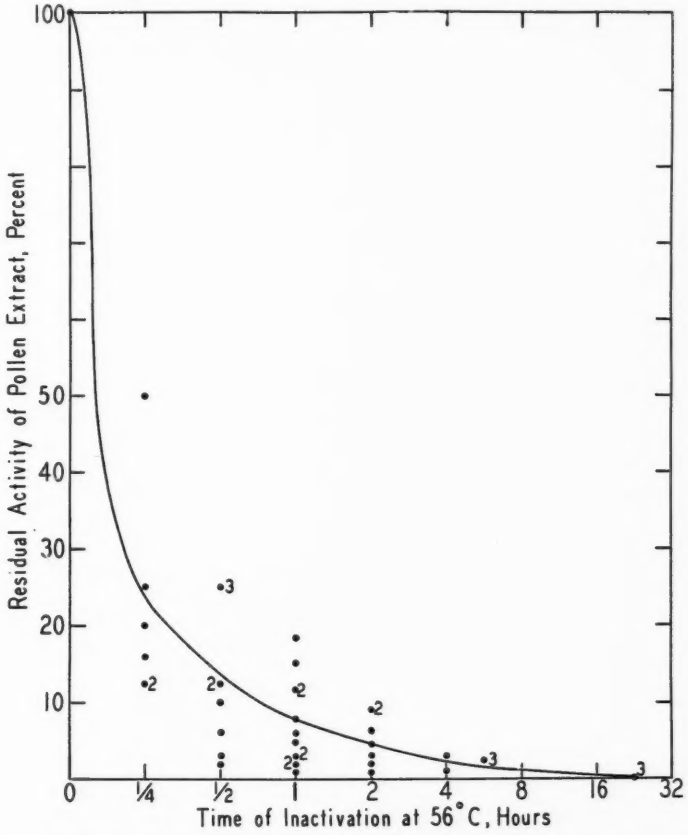

Fig. 1.—The rate of inactivation of short ragweed pollen extracts at 56° C. Summary of 10 experiments similar to that of Table I, with two different extracts, using 10 reagin-containing sera and 21 different recipients. The numbers adjacent to some of the points indicate the number of identical assays. The results with the two extracts were not significantly different, and they are not distinguished in the figure.

*Control experiments indicated that the particular position used on the volar aspect of the arm did not demonstrably affect the results obtained. Similarly, the varying concentration of serum protein in the dilutions of the reaginic serum was found to have no effect on the sensitizing activity of the reagin. This was shown by diluting a reagin-containing serum with both salt solution and normal serum. The highest dilution capable of sensitizing the skin was the same in both instances.

TABLE

RELATIVE REAGIN-NEUTRALIZING ACTIVITY OF FOUR COCA EXTRACTS OF SHORT RAGWEED

DILUTION OF EXTRACT ADDED TO EQUAL VOLUME OF SERUM B. K.	RECIPIENT 380				RECIPIENT 381			
	SERUM B. K. NEUTRALIZED							
	1939	1937	1933	1929	1939	1937	1933	1929
	SIZE OF REACTIONS* OBTAINED WITH 1:100 1939 EXTRACT							
Conc.								
1:2								
1:5								
1:10	0	0	±	5-15	0	0	±	5-20
1:20	0	0	10-25	7-25	0	0	8-30	6-25
1:40	0	6-25	20-40	8-30	0	3-15	12-35	8-30
1:80	0	12-40	15-35	15-40	0	5-25	12-35	10-30
1:160	5-20	12-40	18-40	15-40	0	12-30	15-40	12-35
1:320	5-20	12-40	20-50	22-50	4-15	12-30	15-40	12-35
1:640	6-25	12-40	20-50	22-50	5-25	8-30	15-40	12-35
1:1,280	8-30	12-40	20-50	20-40	8-30	8-30	15-40	15-40
1:2,560								
0 (NaCl control)	10-30							
Minimal concentration of extract necessary to neutralize serum reagin	1:80†	1:20	1:7.5†		1:160	1:20	1:7.5†	
Relative activity of the four extracts referred to unheated extract as 100	100	25	9.5		100	12.5	4.5	

*In the body of the table, the first number refers to the average diameter of the wheal in millimeters, and the second number indicates the average diameter of wheal plus erythema.

†Arbitrarily interpolated between the concentration of extract which completely neutralizes, and that which just fails to neutralize, the serum reagin.

to produce the same result. After one hour at 56° C. the neutralizing concentration of extract was 1:3.5, and after two hours a 1:1.5 dilution was necessary. The relative activity of extracts heated at 56° C. for zero, one-half, one, and two hours was, therefore, 100:25:12:5, respectively. Essentially the same results were obtained in recipient 362.

Ten similar experiments with two different extracts,* 10 different ragweed sensitive sera, and a total of 21 different recipients are summarized in Fig. 1. Identical results were obtained with the two extracts, and they are not distinguished in the figure. The curve in the figure is an arbitrarily fitted best curve. It is apparent that approximately 90 per cent of the reagin-neutralizing activity of these extracts was destroyed within one hour at 56° C.

Rate of Deterioration of Short Ragweed Pollen Extracts at Icebox Temperatures (4° to 8°).—In the light of this rapid inactivation the practical question as to the rate at which pollen extracts deteriorate on storage at icebox temperature was reinvestigated.† Three short rag-

*One was a buffered Coca extract[2] of defatted short ragweed pollen; the other was a simple sodium chloride extract of the whole pollen, previously ground in a low temperature ball mill.[15]

†Although it has been previously reported[10, 16] that extracts stored for a year or more do not react as strongly in pollen-sensitive individuals as do freshly prepared extracts, direct skin testing does not permit a quantitative measure of relative activity.[13]

II

POLLEN, PREPARED IN 1929, 1933, 1937, AND 1939 AND SINCE STORED AT 4° TO 8° C.

RECIPIENT 382				RECIPIENT 387				RECIPIENT 388			
PRIOR TO INJECTION WITH VARYING DILUTIONS OF EXTRACT PREPARED IN											
1939	1937	1933	1929	1939	1937	1933	1929	1939	1937	1933	1929
ON RETESTING PASSIVELY SENSITIZED SITES 24 HOURS LATER											
				WITH 1:40 1929 EXTRACT							
					0	0	0		0	0	0
					0	0	0		0	0	0
					0	0	±		0	0	0
0	0	0	4-15	0	0	±	4-15	0	0	0	3-16
0	0	5-20	5-15	0	0	4-15	4-15	0	0	3-10	3-10
0	0	6-25	6-20	0	0	5-20	4-15	0	0	4-15	5-26
0	5-15	6-25	7-25	0	5-20	8-30	6-25	0	4-15	6-25	5-20
0	6-25	15-40	10-30	0	8-30	8-30	6-25	0	5-20	7-25	5-20
±	6-35	15-40	12-35	0	8-30	8-30	8-30	0	6-25	7-25	7-25
5-15	8-30	15-40	12-40	4-15				5-15			
5-20	8-30	15-40	12-40	6-20				6-20			
				6-25				6-25			
1:240	1:40	1:10		1:320	1:40	1:7.5†	1:3.5†	1:320	1:40	1:10	1:5
100	17	4		100	12.5	2.5	1	100	12.5	3	1.5

weed pollen extracts were available for study which had been prepared by the Coca technique[2] in 1929, 1933, and 1937, from pollen collected no more than six months previously in each instance. These extracts had since been stored at temperatures of 4° to 8° C. The reagin-neutralizing activity of these 3 extracts and of a similar extract freshly prepared in 1939 by the same technique was now determined. The results with five recipients are summarized in Tables II and III. As is there shown, the average relative activities of extracts prepared in 1939, 1937, 1933, and 1929 were 100, 16, 4.5, and 1.2, respectively. The degree of variation in the five individual experiments on which these averages are based is indicated in Table III.

There is no reason to doubt that extracts similarly prepared from different lots of fresh ragweed pollen would differ but slightly in reagin-neutralizing activity. Actually, extracts freshly prepared in 1938 from three different lots of ragweed pollen were almost indistinguishable in this respect. The progressive and striking decrease in the activity of the old extracts is, therefore, in all probability to be ascribed primarily to their age.

It is of interest that despite the marked differences in the reagin-neutralizing activity of these four extracts, there was no significance or regular difference in either their protein nitrogen content or in the ratio $\frac{\text{protein nitrogen}}{\text{total nitrogen}}$ (see Table IV). This is contrary to the

findings of Stull, Cooke, and Tennant,[10, 13] who found that the protein nitrogen content of ragweed pollen extracts had decreased 39 per cent within one year, and that there was a proportionate loss of activity as determined by direct skin tests in naturally sensitive individuals. This was adduced in further support of their thesis that the protein of pollen extracts is the active principle, and that the protein nitrogen content is accordingly an index of the potency of the extracts.

TABLE III

RELATIVE REAGIN-NEUTRALIZING ACTIVITY OF FOUR COCA EXTRACTS OF SHORT RAGWEED POLLEN, PREPARED IN 1929, 1933, 1937, AND 1939 AND SINCE STORED AT 2° TO 8° C.

(Summary of Table II)

RECIPIENT NUMBER	RELATIVE REAGIN NEUTRALIZING ACTIVITY OF EXTRACT PREPARED IN:			
	1939	1937	1933	1929
380	100	25	9.5	<9*
381	100	12.5	4.5	<5*
382	100	17	4	<4*
387	100	12.5	2.5	1
388	100	12.5	3	1.5
Average reagin-neutralizing activity of the four extracts referred to that of the 1939 extract as 100	100	16	4.5	1-1.5 (approx.)

*The data of Table II do not permit quantitative determination; no neutralization in highest concentration used (1:10).

TABLE IV

FOUR SIMILAR RAGWEED EXTRACTS PREPARED IN 1929, 1933, 1937, AND 1939 DID NOT SIGNIFICANTLY DIFFER IN THEIR TOTAL NITROGEN AND PROTEIN NITROGEN CONTENTS

EXTRACT PREPARED IN	TOTAL NITROGEN CONTENT	PROTEIN NITROGEN CONTENT	RATIO OF PROTEIN NITROGEN / TOTAL NITROGEN
	*Mg./c.c.**	*Mg./c.c.**	*Per cent*
1929	0.75	0.23	31
1933	0.63	0.21	35
1937	0.68	0.22	32.1
1939	1.1	0.29	26.1

*All figures are averages of at least three determinations, which checked within satisfactory limits of experimental error. The method used for protein nitrogen was that used by Stull, Cooke, and Tennant.[10]

The present findings, on the other hand, indicate that the protein nitrogen content is an unreliable measure of the biologic activity of ragweed pollen extracts. This does not necessarily imply that the active constituent in pollen extracts is nonprotein in character. The hypothetic reactive protein may constitute only a negligible proportion of the total protein in the extract. Moreover, the reactive protein may completely lose its biologic activity and yet remain precipitable by sulfosalicylic acid or other protein precipitants.

Thermolability of Atopic Ragweed Reagin.—Coca and Grove[11] were apparently the first to find that heating atopic reagin for one-half hour

at 56° C. markedly diminished its sensitizing power. No quantitative data were presented as to the degree of inactivation, nor was it stated whether the criterion of inactivation was the smaller size of the skin reactions obtained on retesting the passively sensitized sites, or the increased amount of serum necessary to sensitize. Gay and Chant[12] also found reagin to be thermolabile at 56° C., as evidenced by a decrease in the size of the wheal obtained on retesting passively sensitized sites. The area of redness produced in these sites was, however, not decreased; and their method did not permit a quantitative evaluation of the degree of inactivation.

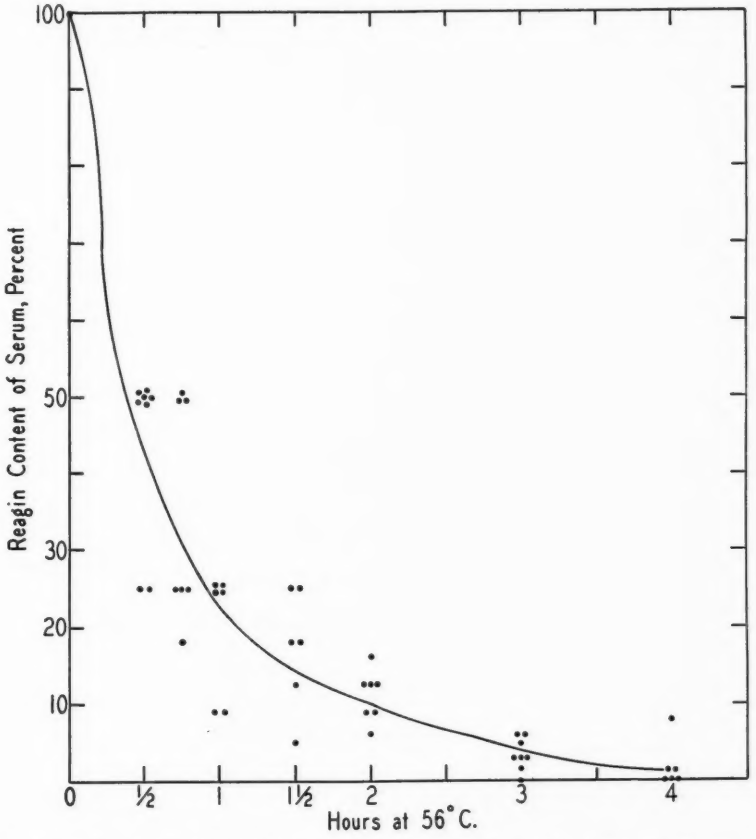

Fig. 2.—The rate of inactivation of atopic ragweed reagin at 56° C. Summary of 10 experiments similar to that of Table IV, with nine different ragweed sensitive sera and 21 recipients. The curve in the figure is an arbitrarily fitted best curve.

Our own experiments on this point are summarized in Table V and Fig. 2. In the experiment of Table V the unheated serum T. B. was capable of sensitizing the skin of recipient 345 when used in a dilution of 1:320, and in a dilution of 1:80 after heating for three-fourths hour at 56° C. After heating at 56° C. for one and one-half hours, the serum could sensitize the skin only in a dilution of 1:20, while after three

TABLE V

THERMOLABILITY OF SHORT RAGWEED POLLEN REAGIN AT 56° C.

DILUTION OF SERUM T.B. USED TO SENSITIZE SKIN SITES	RECIPIENT 345				RECIPIENT 346			
	SITES SENSITIZED WITH							
	UNHEATED SERUM	SERUM HEATED AT 56° C. FOR			UNHEATED SERUM	SERUM HEATED AT 56° C. FOR		
		¾ HOUR	1½ HOURS	3 HOURS		¾ HOUR	1½ HOURS	3 HOURS
	SIZE OF REACTIONS* OBTAINED ON RETESTING PASSIVELY SENSITIZED SITES 24 HOURS LATER WITH 1:100 SHORT RAGWEED POLLEN							
Conc.			7-25	7-25			8-30	6-20
1:2				0				5-15
1:5			7-25	0			8-30	3-10
1:10		10-30	8-30	0		12-40	10-30	0
1:20	12-40	10-30	6-25	0	12-40	10-35	8-30	0
1:40	7-25	7-25	0	0	10-35	10-30	0	0
1:80	7-20	6-20	0	0	10-35	0	0	0
1:160	5-20	0	0	0	7-25	0	0	0
1:320	3-10	0	0		0	0	0	0
1:640	0	0			0	0		
1:1,280	0	0			0	0		
1:2,560	0				0	0		
Highest dilution of serum capable of sensitizing skin site	1:320	1:80	1:20	1:1	1:160	1:40	1:20	1:5
Relative skin sensitizing activity referred to unheated serum as 100	100	25	6	0.3	100	25	12.5	3

*In the body of the table the first number refers to the average diameter of the wheal in millimeters, and the second number refers to the average diameter of wheal plus rythma.

hours at 56° C. sensitization was observed only with the whole serum. It is important to note that the same extract in the same dilution and in the same amount was used to test all the passively sensitized sites.

Ten similar experiments with nine different ragweed sera chosen at random and 21 recipients are summarized in Fig. 2. The curve in that figure is an arbitrarily fitted best curve. It indicates that approximately 50 per cent of the reagin in human atopic serum is destroyed in one-half hour at 56° C., 75 per cent in one hour, 90 per cent in two hours, and more than 98 per cent in four hours.

SUMMARY

Ragweed pollen extracts have been found to be highly thermolabile. Approximately 75 per cent of their reagin-neutralizing activity is destroyed within fifteen minutes at 56° C., 90 per cent within one hour, and over 95 per cent in four hours.

The reagin-neutralizing activity of four similar ragweed pollen extracts prepared in 1939, 1937, 1933, and 1929 and since stored at 4° to 8° C. were found to be as 100:16:4.5:1.2, respectively, indicative of a

fairly rapid deterioration. Despite the widely differing biologic activities of these four extracts, their protein nitrogen contents, and the ratios of $\frac{\text{protein nitrogen}}{\text{total nitrogen}}$, were of the same order of magnitude. This does not necessarily exclude the possibility that the reactive constituent is a protein.

Short ragweed pollen reagin has also been found to be highly thermolabile. On heating at 56° C. approximately 50 per cent of the skin-sensitizing activity was destroyed within one-half hour, approximately 90 per cent within two hours, and approximately 99 per cent within four hours.

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TIME REQUIRED FOR THE PRODUCTION OF HAY FEVER BY A NEWLY ENCOUNTERED POLLEN, SUGAR BEET

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THIS paper reports the behavior of a group of allergic persons when they were exposed in successive years to the pollen of the sugar beet, which they had never before encountered.

The sugar beet is a variety of the domestic beet, *Beta vulgaris,* specialized to produce a high content of saccharose. Botanically it belongs among the chenopods. It is grown extensively in various parts of the West, the industry being aided by a differential tariff. In cool climates it is customary, in producing beet seed, to dig up the mature beets ("mother beets") in the fall, store them away from frost, and replant them to go to seed the next spring. In the Phoenix district the entire cycle can be completed in eight months, with half the labor. The seed is planted in October, the half-grown plant is not winterkilled, and the seed is ripe for harvest in June. This having been demonstrated by experiment, the industry was introduced in 1936, when some 1,800 acres were planted. The following year there were 3,200 acres in beets, and in 1938 the beet crop occupied 5,500 acres, all of which went to seed.

The beets are planted in rows, and their growth is so rank that each row resembles a hedge. In late April and May, when they bloom, the plants are from 3 to 6 feet high. They have a sickening sweetish perfume that can be smelled a long distance. Their pollen production is enormous.

I obtained some beet pollen from the 1936 crop, and in 1937 I tested twenty-nine hay fever patients with it. There were twenty-one positive reactions, none very strong, and all in persons sensitized to the other local representatives of the Chenopodiales. At the time these tests were made, there was considerable beet pollen on the air, along with pollen of the biologically related Palmer's amaranth and Russian thistle. As an experiment, beet pollen was included in the coseasonal treatment of six of the patients reacting to it. These patients had satisfactory relief, but so did the other beet reactors who received none of this pollen. I concluded that the beet reaction was merely another example of the group sensitivity that is common among chenopod-sensitive persons. The error of this conclusion was not revealed until the following year.

In the spring of 1938 the pollen clinic was treating about the usual number of patients for this season: some hundred-odd patients under treatment, two-thirds of them having been treated the previous year; a few late-comers with symptoms still uncontrolled; a few complicated

cases with incomplete relief; and all the rest comfortable and tapering off their treatment for the summer. Early in May this pleasing picture changed abruptly. Patients who had been free from symptoms, and who properly expected to remain so, began to come in with florid hay fever. They insisted that some new pollen was on the air, and they were right. A hasty resort to slides showed the preponderance of chenopod pollen. Russian thistle and amaranth were present, of course, but more abundant than either was the compact granule of the sugar beet. Notwithstanding its insignificant performance of the year before, retesting with beet appeared to be in order.

There was in the refrigerator a 1:500 dilution of sugar beet pollen, made up a year earlier. When fresh, this reagent had elicited only moderate reactions. Three patients with recurrent hay fever received 0.02 c.c. intradermally. The prompt application of tourniquets prevented constitutional reactions, but two of the three could not use their tested arms for a day or two. Fresh solutions of lower strength were prepared and used in testing all patients. This was an opportunity, not often available, to examine the reactions of allergic persons exposed to a new pollen, artificially introduced, and with a known period of contact.

In May, 1938, 138 hay fever sufferers, all residing in the Phoenix district, were tested intradermally with about 0.02 c.c. of a 1:5,000 dilution of sugar beet pollen, with the following results:

Four patients reacted to sugar beet and to no other pollen. One of this group had been by reason of his occupation selectively exposed; he was an entomologist specializing in the study of insect parasites of the beet. The others were children in their first season of hay fever.

One hundred and five patients, sensitized to the pollens of amaranth and Russian thistle, reacted to sugar beet as well. As a rule, the beet reaction was the strongest of the three. Nineteen patients, sensitized to amaranth and Russian thistle, did not react to beet.

Ten patients, sensitive to grass pollens, reacted neither to beet nor to the pollens of the other chenopods.

From the evidence of these skin tests it appears that the sugar beet has, in addition to the group atopen common to the Chenopodiales, a highly potent specific atopen of its own.

This impression is strengthened by an examination of the treatment records. Of the 138 patients tested with sugar beet, the records of 96 were available for the corresponding season in 1937. Of this number, 37 experienced a sharp upset or relapse in May, 1938. All of these had been adequately protected against amaranth and Russian thistle; all but one had been comfortable under similar treatment in the corresponding month of the preceding year. When these relapsing patients were treated with sugar beet, thirty of them obtained prompt relief, some with the first dose, and none required more than four doses to relieve

their symptoms. The reason for failure in the remaining seven is not relevant to this discussion, but in four cases it was so odd that it is worth recording. They were eating honey. A syndicated health column had reviewed an article advocating the use of honey to cure hay fever. These four patients had been giving this agreeable home remedy a good trial. Their honey was stopped, and with it, their hay fever.

As soon as the cause of the first crop of relapses was identified, sugar beet was incorporated into the treatment of all who showed skin sensitivity to this pollen. None of those so treated suffered a relapse. It seemed quite clear that the late seasonal upset was caused by the pollen of the beet, and that, as a rule, an adequate hyposensitization against the allied amaranth and Russian thistle did not afford protection against beet. Observations showed that beet pollen was abundant on the air during the entire month of May, 1938, and some could be found until the middle of June. It was possible to learn with considerable accuracy the blossoming time in the preceding year; it was practically the same. This, with the acreage, shows the approximate exposure required to produce clinical evidence of sensitivity in this allergic group.

The experimental patches in 1935 can be disregarded. In 1936, the 1,800 acres planted must have put considerable pollen on the air, and its distribution was spread over about two months because the ranchers did not know exactly when to plant to secure the best yield. In 1937 there were 3,200 acres, all planted to bloom in May. This worked out profitably, and the nearly doubled planting of 1938 pollinated in the same month, with discomfort to a large number of hay fever victims. Two years of preparation, with an adequate exposure in the third year, were required to elicit symptoms. In the current year of 1939, at least an equal number react sharply to beet but are protected by a preliminary dosage. Two years of seasonal contact seem to have been the time required to develop clinical evidence of sensitivity to the newly encountered pollen.

SUMMARY

A group of allergic persons was exposed in successive years to the pollen of sugar beet as the result of the introduction of a new industry into the region where they resided. They had never before encountered this pollen.

No tests were made with beet pollen during its first year of prevalence. In the second year positive skin tests were observed with no definite manifestations of clinical sensitivity to beet pollen. In the third year skin tests were strongly positive, and intense symptoms of pollinosis occurred in a considerable number of the patients under observation.

Individuals clinically sensitized to the pollens of other chenopods were found to be especially liable to acquire sensitivity to beet pollen;

but the treatment that protected them against the pollens of amaranth and Russian thistle did not provide a defense against sugar beet pollen. The sugar beet has, in addition to the group atopen common to the Chenopodiales, a potent atopen of its own.

A few doses of sugar beet pollen extract, when supplemented by the immunity conferred by treatment with other pollens, promptly controlled the pollinosis induced by sugar beet.

In this series of cases, two seasons of exposure to a newly encountered pollen were required to induce clinical sensitivity to that pollen.

THE TRANSFERENCE OF REAGINS IN BLOOD TRANSFUSIONS*

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IN THE PAST two years I have had an opportunity to study the effect of blood from allergic donors upon nonallergic recipients.

The first donor was a physician, 29 years of age, who developed hay fever for the first time about the middle of August, 1936. There were no known allergies in his family. The diagnosis was perennial allergic vasomotor rhinitis with seasonal exacerbations due to weed pollens. The patient was tested and found to be skin sensitive to house dust, chocolate, string beans, spinach, and ragweed pollen. These foods were eliminated, house dust was reduced in his living quarters, and he was hyposensitized with an extract of house dust and ragweed pollen. His perennial symptoms entirely disappeared, and he obtained satisfactory relief from his pollen hay fever.

This patient acted as the blood donor for two recipients whom I was able to study. These recipients had no history of allergic diseases themselves, nor were there any in members of their families so far as could be determined by history. Both patients had a marked secondary anemia, and the diagnosis in each was carcinoma.

Before transfusion the recipients were skin tested to all of the substances, except house dust, which gave positive reactions in the allergic donor. The skin tests of the recipients were negative to these substances. After the transfusions of 500 c.c. of whole blood from the allergic donor, the recipients were again tested to the same substances; it was found that they reacted to ragweed, string bean, and spinach. These substances which gave positive reactions by direct testing on the donor's skin also gave positive reactions with his blood by the Prausnitz-Küstner technique of passive transfer. The reactions in the recipients were maximum in four to five days and remained positive for about two weeks. After this time they were faint and difficult to interpret.

Chocolate was negative by direct test on the recipients and also negative by passive transfer.

Although the donor was clinically and skin sensitive to house dust, this antigen was not used to test the recipients because of the difficulty of distinguishing a specific from a nonspecific reaction.

Another physician who had late hay fever since the age of nine was skin sensitive to house dust, orris root, horse, and timothy and ragweed pollen. He acted as a blood donor for a recipient who had a

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carcinoma of the stomach. The recipient gave no history of personal or familial allergy. His skin tests were negative to the above allergens before the transfusion.

Fourteen hours after a transfusion of 500 c.c. of whole blood from the allergic donor to the nonallergic recipient, the recipient's skin showed slight reactions to house dust and ragweed. In four days the recipient's skin reacted as follows:

House dust	Marked
Orris root	Moderate
Horse	Moderate
Timothy	Moderate
Ragweed	Marked
Egg (control)	Negative

On the sixth day the tests were not quite as large as they were two days previously.

All of the tests on this recipient, before and after the transfusion, were done with the same syringes without refilling them.

Blood from this donor showed reagins for house dust, horse, and timothy and ragweed pollens. Orris root, on the other hand, which reacted on the recipient after the blood transfusion and on the donor by direct test, gave no reaction on passive transfer with the donor's blood.

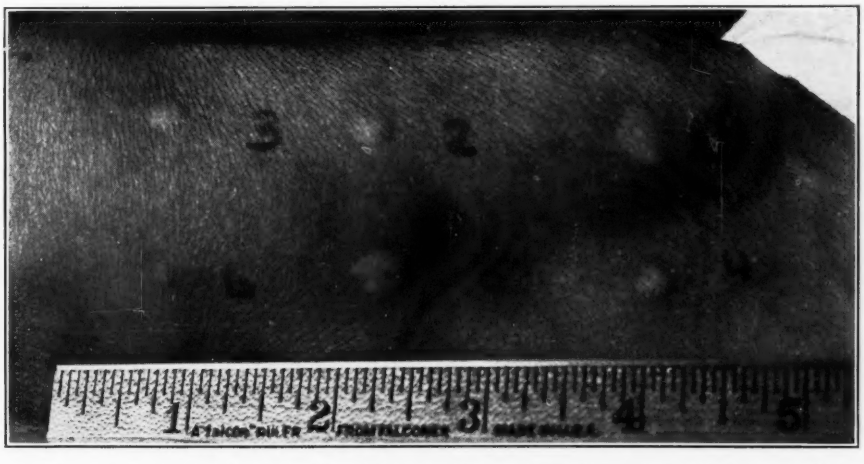

Fig. 1.—Tests obtained in the third nonallergic recipient six days after blood transfusion from an allergic donor. *1*, House dust; *2*, orris root (0.01 mg. N); *3*, horse dander (0.001 mg. N); *4*, timothy (0.01 mg. N); *5*, ragweed (0.01 mg. N); *6*, egg (control).

DISCUSSION

It has been demonstrated in these 3 cases that it is possible passively to sensitize the skin of a nonallergic recipient by means of a transfusion of 500 c.c. of whole blood from an allergic donor. No attempt was made in any of these cases to demonstrate a clinical sensitivity.

Ramirez[1] reported one case of passive sensitization. The recipient had primary anemia and received 800 c.c. of blood from a horse dandruff-sensitive individual. Two weeks later the recipient developed asthma when exposed to horse dandruff. The recipient's skin was not tested before the transfusion and there was no mention made of the skin test after depletion of the passive sensitization. In other words, it is not clear whether or not this was a true passive sensitization.

Mills and Schiff[2] reported the case of a hemophiliac who developed a "typical protein reaction" at the site of a test to horse serum thirty minutes after he had received 800 c.c. of blood from a known horse-sensitive individual. The skin test to horse serum before the transfusion was negative. This instance is not as clear-cut as those reported here because the patient had been given 4.0 c.c. of horse serum subcutaneously eight days previous to the transfusion.

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ATTEMPTS TO DETECT A REACTION BETWEEN HUMAN ALLERGIC SERUM AND ITS ANTIGEN*

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THE nature of the reaction between an antibody and its antigen in human allergy is obscure and the only known means of studying it experimentally is by passive transfer, for the reason that serologic reactions, such as are usually found in artificially immunized animals, are lacking. Cooke, Barnard, Hebald, and Stull[1] found no evidence of a binding of antigen by the skin-sensitizing antibody. On the other hand, Albus[2] found a slight inhibition of the hemolysis of sheep cells by allergic human sera when extracts of the pollen to which the patient was sensitive were added.

Certain methods of physical chemistry offer possibilities for studying the reactions between proteins. Especially valuable for such studies are the ultracentrifuge[3] and the Tiselius electrophoresis apparatus.[4] These instruments were used in an attempt to detect a physical union between the antibody in human allergic serum and its antigen.

The human serum was from a person sensitive to rabbit hair and to rabbit serum. Large marked reactions were obtained by intracutaneous testing with rabbit hair extract containing 10 protein units (0.0001 mg. protein nitrogen) per cubic centimeter or with rabbit serum diluted 1:1,000. The human serum was very active in passive transfer. The person had been treated in the past, for a period of two years, by injections of rabbit hair extract with but little relief, but had not had treatment in the two years immediately preceding the experiments described here.

In the first experiment the human serum was mixed with an equal volume of the 10 protein unit rabbit hair extract. This mixture was centrifuged at 100,000 times gravity in an air-driven ultracentrifuge for three hours. Samples were then pipetted from the top, middle, and bottom of the centrifuge cup and tested for the presence of rabbit hair protein by intracutaneous tests. The protein was found in all samples, showing that it had been thrown down little, if any, by the centrifuging. The antibody could not be detected directly, but the antitoxin to staphylococcus, which is the same sort of protein,[5] was found in samples from the middle and bottom only. Thus it would appear that, in this case, no union had taken place between the antibody and the allergen.

Experiments for the same purpose were carried out using the Tiselius electrophoresis apparatus. The human serum was first fractionated in the apparatus to separate the antibody-containing globulins from the

*From the Biochemical Research Foundation of the Franklin Institute, Philadelphia.

albumin. These globulins were then mixed with albumin, separated by electrophoresis, from rabbit serum. The components of this mixture migrated at different rates when an electric current was passed through the solution. The migration was followed in the Tiselius apparatus by observing the refraction of a light beam passing through the mixture. Dark boundaries were seen between the components that separated. No new boundaries were found, so that there was no evidence of a new compound being formed by the human antibody and the rabbit albumin. No quantitative determinations were made in this experiment, but skin tests showed the rabbit protein to be strong in the faster migrating portion and weak in the slower portion, while precipitation tests showed just the opposite distribution for the human protein.

In a second test a scale was photographed through the apparatus while the electrophoresis was being carried on. Differences in concentration caused a deviation of the beam of light. The scale was distorted, and some of the individual lines were displaced. Measurement of the distances by which the lines were displaced from their original positions permitted an estimation of the difference in concentration of the components of the mixture. Plotting the displacement of the lines resulted in curves with peaks for albumin and three globulins: alpha, beta, and gamma. Tiselius and Kabat[6] used this method to study immune sera and published a graph of the scale deviation curves for anti-egg albumin rabbit serum before and after absorption of the antibody. These authors found the only change to be a great diminution in the size of the peak which corresponded to gamma globulin. Antibody is the main constituent of the latter serum protein.

In the present experiment the whole human serum was mixed with an equal volume of a solution of the albumin from rabbit serum (5.4 mg. protein per c.c.). An electrophoresis run was made, and the displacement of the scale was measured and plotted. Similar runs were made with corresponding dilutions of human serum and of rabbit albumin separately as controls. No significant differences were found between the curves for human serum alone or mixed with rabbit albumin, except that the peak for albumin was increased by the amount of the rabbit albumin. Thus again no evidence was found of a physical union between allergic antibody and its antigen.

SUMMARY

Mixtures of a serum from a human being sensitive to rabbit hair and rabbit serum were made with these antigens, and the mixtures were studied by means of the air-driven ultracentrifuge and the Tiselius electrophoresis apparatus to detect evidences of physical reaction between the antibody and the antigen. No such evidence could be found

under the conditions of the experiments. These negative findings support the belief that in human allergy there is no physical reaction between the antibody and its antigen in the blood.

The author wishes to express his gratitude to Mr. Thomas J. Dietz and Dr. Laura E. Krejci, of the Physico-chemical Department, for their cooperation.

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Special Report

NOTE ON ORAL POTASSIUM CHLORIDE THERAPY IN ASTHMA, HAY FEVER, URTICARIA, AND ECZEMA*

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EXCELLENT clinical results in the treatment of urticaria and hay fever by the administration of potassium salts by mouth have been reported by Rusk and Kenamore[1] and by Bloom.[2] This line of therapy would appear to have been based on the pharmacologic similarities of potassium and adrenalin and on D'Silva's discovery that the injection of adrenalin in animals is attended by a rise in the serum potassium due to the liberation of potassium from the liver. Hypothetically, the alleviating effect of adrenalin in allergic diseases is due to the action of the potassium thus liberated.

The present note reports the results obtained with oral potassium chloride therapy in hay fever (10 cases), allergic rhinitis (10 cases), asthma (10 cases), urticaria (9 cases), and eczema (4 cases).

TABLE I

RESULTS OF TREATMENT

CONDITION	NO. OF CASES	AVG. DURATION OF TREATMENT	RESULTS			
			MARKED IMPROVEMENT	MODERATE IMPROVEMENT	NO IMPROVEMENT[a]	WORSE
Hay fever (grass)	10	2. weeks	0	0	6	4[b]
Allergic rhinitis	10	3.8 weeks	2[c]	1	5	2
Asthma	10	2.7 weeks	0	0	7	3[d]
Urticaria	9	3.8 weeks	1[e]	1[f]	6	1
Eczema	4	3.5 weeks	0	1	3	0

[a]Approximately 50 per cent of the patients (excepting the hay fever ones) reported slight or definite improvement during the first one or two weeks of the treatment but relapsed on continuing it.

[b]Pollen cloud was heavier during the period of treatment.

[c]One patient relapsed in three weeks and failed to respond to a second course of potassium chloride.

[d]Probably due to stopping other medicinal treatment during the experiment.

[e]Strong psychologic factor (sexual) precipitating the attacks.

[f]Relapsed in four weeks but responded very favorably to a course of *sodium* chloride tablets, 5 grain, three times a day, in water.

*From the Inoculation Department, St. Mary's Hospital, London.

Following the method employed by Bloom, one 5 grain tablet of potassium chloride dissolved in a glass of water was given one-half hour before meals, three times a day.

CONCLUSION

Oral potassium chloride therapy, in the dosage employed, failed to produce a significant degree of improvement in a group of 43 allergic patients.

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Society Proceedings

SYMPOSIUM ON ALLERGIC DERMATOSES*

MARION B. SULZBERGER, M.D., PRESIDING

Contact-Type Eczematous Dermatitis. MARION B. SULZBERGER, M.D., New York, N. Y.

The contact-type eczematous dermatitis, which is the subject of my part of this discussion, is probably the most common of all allergic dermatoses. I think one can say more than that. It is possibly the most common of all diseases of man and surely of all allergic diseases of man.

The frequency of this dermatosis will become apparent to all of you if you consider that there is scarcely anyone who has not had either a poison ivy dermatitis, or some other plant dermatitis, or a dermatitis caused by some external irritant, or an eczematous dermatitis due to fungi in the groin or between the toes. All of these are, in their mechanism and pathogenesis, simply common forms of eczematous contact-type allergy; thus, I think it is safe to say that this is a disease which is perhaps second, if not equal, to the common cold in frequency. Not only that, but of all the conditions which affect man, this dermatosis is the one which has been the most conclusively proved to be of allergic character. In other words, it is one of the few diseases in which the cycle of proof has been completed, in which one has been able deliberately to expose individuals to certain substances, to observe that these substances on first exposure produce no eczematous reactions, and to note the time required for an incubation period to elapse. By a re-exposure of the individual's skin to the same substance in the same concentration and manner, the actual eczematous disease is produced and the effect is proved to be a specific one; all these are links in the chain of proof that a specific sensitization has taken place. So we can say that eczematous contact-type dermatitis is extremely common and that, in most instances, it can be proved to be allergic.

This does not mean necessarily that eczematous dermatoses which are not allergic do not occur. The definition of an eczematous dermatosis is based upon its morphology and not upon its causal mechanism. Just as there are allergic dermatoses which are eczematous and those which are noneczematous, so there are eczematous dermatoses which are not allergic and those which are allergic. To give some examples of the

*Presented at the Seventeenth Annual Meeting of The American Society for the Study of Allergy, St. Louis, Mo., May 15, 16, 1939.

former, I may mention the typical dermatosis produced by certain degrees of sunburn; this is known as eczema solare, but is not an *allergic* eczematous dermatosis; moreover, there are the eczematous dermatitides which are due, not to allergens, but to primarily irritating substances, such as caustics, acids, alkalies, etc.; and there are the eczematous reactions from physical agents such as heat, friction, and maceration. All these are examples of eczematous dermatitis on a nonallergic basis.

However, in the usual form of eczema in which allergy is the sole mechanism or an important contributory mechanism, the causal agents are allergens. These substances produce disease because they are able to sensitize. A rather new concept concerning the nature of allergens is introduced when we realize that the causal substances in this most common and best proved of human allergies are allergens of small molecular weight and are not proteins or substances necessarily associated with proteins. Even elements such as mercury, nickel, arsenic, etc., are among the specific sensitizing agents in eczematous allergy, and certain individuals will be sensitized to these particular elements regardless of the combination in which they appear.

Another noteworthy fact is that causal agents of an eczematous form of allergy are usually the substances which can most easily attain access to the living tissues of the skin; in other words, they are those substances which can penetrate through the natural protective layers of cornified material, lipoids, and sebum at the skin surface. Consequently, common eczematogenous allergens are very often either fat solvents, substances soluble in fats (like the oil-soluble excitants of many plant dermatitides), or substances which are keratolytics or detergents which remove the outer protective layers of the skin's surface.

The diagnosis of eczematous contact-type dermatitis depends first of all upon the history, the clinical appearance, and the course of the eruption. A search for the causal agents depends on: first, the history; second, the localization and appearance; third, the subsequent course; and, *only in the last analysis, upon the skin test.* If you will realize that the patch test used in investigating this form of dermatosis has the same advantages and the same drawbacks as other forms of skin testing, you will know about all I need tell you of the evaluation of patch tests. One may get negative results to patch tests with substances that have caused the clinical disease and positive results to patch tests with substances which have nothing at all to do with the presenting clinical disease. For these and other reasons, the results of the tests cannot be conclusive; like all other skin tests, patch tests must be correlated with the other data you obtain in the case.

The treatment of this form of dermatosis is, like the diagnosis, *dermatologic* in the first place. The only successful approach from the point of view of allergy is the elimination of the causal agents. This

is very easy in some instances and extremely difficult in many others; in quite a few cases, elimination of causal allergens unfortunately is impossible.

Many of the causal allergens which produce eczema are so ubiquitous and so constantly and universally encountered that it is absolutely impossible to eliminate them entirely. In such instances it is only in patients with lesser degrees of sensitivity that one can reduce the exposure sufficiently to bring clinical relief.

One word about desensitization, which I said was generally ineffectual. There seems to be some clinical evidence that in some forms of contact-type eczematous dermatitis (for instance, in cases due to plant oils) desensitization is effective. However, even this question is very much up in the air. All my attempts to show—experimentally and scientifically, by repeated quantitative serial patch tests—that a desensitization of the skin has been achieved by means of specific injections in contact-type dermatitis due to plants have thus far failed. In studies that I and my associates carried out, the skins of the individuals, after receiving specific injections, were just as sensitive to quantitative patch tests as they were before the injection or as sensitive as those of a control group which received placebo injections.

I have deliberately called these eczematous eruptions the "contact-type" because, while they are usually due to external contact, they can sometimes be caused by excitants which come from within. If the causal allergens reach the specifically sensitive, superficial, cutaneous shock tissue (epidermis?) in sufficient quantities—that is, if a sufficient concentration reaches the shock tissue per unit of time and per size of skin area—the contact-type dermatitis will be produced even from within. This is the case in eczematous eruptions which appear after the injection or ingestion of quinine, urotropin, arsenicals, plant excitants, etc., to mention only a few of many possible examples.

DISCUSSION

DR. SULZBERGER.—I should now like to call upon you to discuss what I have just said for a few minutes before going on to the next subject. I should like the gentlemen assisting me at the table here to participate and perhaps break the ice by questions or by additions to what I have just tried to outline.

DR. HARRY ALEXANDER, St. Louis.—If it is not out of order for the president to ask a question, I should like to inquire how many contactants thus far have been discovered or employed.

DR. SULZBERGER.—Recently Dr. Rostenberg, Jr., and I published a list of substances used in patch testing and the concentration to be employed, based on our own experience and on the findings in the literature.* I think there were 740 different substances in that list. These were by no means all the substances which were known to cause

*J. Invest. Dermat. 2: 93, 1939.

contact-type eczema, but were merely those substances which had been sufficiently employed and sufficiently studied to enable us to say that certain concentrations were not primarily irritating and were the correct ones for patch testing. I am sure that Dr. Schwartz, for example, could add a great number to that list, if he were to include all the substances he has known to cause occupational eczematous dermatitis.

Dr. Louis Schwartz, New York.—I have classified the chemicals which have caused contact dermatitis, and under that classification can be included thousands of different ones. I have also classified a list of materials with which I have done patch tests in industry; I have published that list showing the concentrations of these substances with which I have made patch tests and produced reactions in people who had dermatitis and the concentrations with which I did not produce reactions in those who worked at the same job, but who did not have dermatitis.

These concentrations are not minimal; they are not threshold concentrations. They happened to be the concentrations I used at the time upon the advice of the chemists and technical men in the factory as trial solutions, and with which I produced positive patch tests in the workers who had dermatitis and negative reactions in the controls.

That list was published in one of the numbers of the *New York State Medical Journal* and can be obtained by writing to my office.

It remains for the rest of you gentlemen to try to work out minimum cancentrations that can be used, although I think that that is a very difficult problem because the concentration that will produce a reaction in one person may not in another. A concentration of 1:1,000 may produce a reaction in a person who is very sensitive, whereas 1:500 or 1:100 may produce a reaction in another person not as sensitive as the first one. Therefore, I think minimal concentrations are very difficult, if not impossible, to work out for patch testing.

Dr. Samuel J. Taub, Chicago.—What is the ideal time for putting on a patch test, and what about the site on the skin? I mean that the skin is variable in its reactions to the patch test. You may have a substance applied that is really the causative agent; if applied, for example, on the back, it may not react at all, whereas, if you patch test with the same substance at the time that the contact dermatitis is cleared up and in the area where it has occurred, your results will be altogether different, will they not?

Dr. Sulzberger.—That is an important point, for it is one of the reasons for a false negative patch test, i.e., for obtaining a negative patch test despite the use of the agent which actually caused the trouble. The skin is variable in its capacity to react to these eczematogenous substances. In the first place, one can demonstrate variations due to the passage of time. At one time the entire skin may be hypersensitive, and at other times not. Often there is a phase of desensitization for several weeks following an acute attack of dermatitis. And there are also times at which the skin is refractory. Moreover, there are variations in the degree of sensitivity in different skin areas. In some persons some sites are very much more sensitive than others. Sometimes this variation depends upon the physical properties of the skin surface, or upon the amount of horny layer, grease, or sweat; and sometimes this variation depends on a true immunologic difference in degree of allergic change.

An example of this latter type was published by Dr. Field and me. We studied a patient sensitive to poison ivy in whom a dollar-sized area on the forearm did not share in the sensitivity. There was no preceding injury or anything else known to have caused the difference in sensitivity of this particular site.*

As a rule, the most sensitive sites, and therefore, in some ways the best to test, are, just as you said, the sites in which a preceding dermatitis has appeared and has abated, always with the allowance of a sufficiently long interval for the possible refractory phase to pass and for the sensitivity to reappear. Stauffer of Zürich demonstrated this point most clearly in a series of tests for occupational dermatoses. In many of his cases an actual causal substance did not produce reaction unless the patient was tested on a previously affected site some time after the occupational eczema had been healed.

As a rule, one can say that the nearer to the area of original dermatitis the patch tests are placed, the greater the likelihood of getting a positive reaction. But there is here the same objection as in other forms of skin testing. It is not always best to have a test which is too delicate, too sharp, like certain serologic reactions in syphilis. One then runs the risk to too many false positives. One must try to standardize one's tests to be sufficiently sensitive to give positive reactions in the cases in which the clinical evidence demonstrates that the particular substance caused the dermatosis, and yet not so delicate as to give many positive reactions in people who are not suffering from clinical sensitivity to the respective allergens. So, the important thing in putting on patch tests is not only the concentrations and the vehicles which you employ, not only the sites which you select for testing, but also the use of a standardized procedure. At present the only adequate means of standardizing a test procedure is to try it upon a sufficient number of individuals with a dermatosis from the substance and upon a sufficient number of control individuals without dermatosis from the substance. Only after this has been done can one say that with a certain test and with a certain substance the reaction has this or that probability of having clinical significance. As far as I know, the orthodox patch test method is the only one which is today backed by sufficient experience for us to have definite information on the varying significance of reactions to a large variety of substances and concentrations.

DR. FRANCIS M. RACKEMANN, Boston.—It is easy to get the impression that those agents which cause contact dermatitis are soluble in fat or oil. Is that correct?

DR. SULZBERGER.—In fat, oil, or water.

DR. RACKEMANN.—In water also? I wanted to call attention to that double role because, in the case of ragweed, where we have the data accurately, the dermatitis depends upon the fat-soluble portion of the ragweed, and scratch tests with the water-soluble portion are negative. In the nickel cases, on the other hand, the reaction is obtained by a watery solution of nickel. I wonder if Dr. Sulzberger has theories that would help us explain why it is sometimes the oil and sometimes the water.

DR. SULZBERGER.—In some of my articles I have mentioned theories about that, Dr. Rackemann, but I do not think any of them would be of

*J. ALLERGY 7: 139, 1936.

much help to you. Dr. Schwartz also has expressed theories concerning that point. We both believe that the tendency to develop certain forms of sensitivity may depend to some degree upon the chemistry or the physical properties of the skin surface. Perhaps seborrheic persons, who tend to protect themselves with more oil at the skin surface or who have a greater protective covering of oil, are less likely to become sensitized by water-soluble substances than are individuals with dry skins. One does not know the answer to these questions yet; but the fact is that contact-type excitants can be either oil- or water-soluble. Among the many water-soluble eczematogenous allergens are the ones you have mentioned and also such agents as nickel salts, formalin, mercury salts, etc.

DR. J. GARDNER HOPKINS, New York.—One thing else—we think that all these contact agents are partial antigens, and it probably is true that they cannot sensitize us until they have combined with protein. There are indications that in order to produce contact dermatitis the causal agent must be capable of two things: it must get through the horn and oil of the outer epidermis and probably must combine with a body protein. The water-soluble allergens of which you have spoken are very often substances which react very actively with proteins such as mercury, iodine, and formalin; I am not sure about nickel.

I doubt if there is any proof whether or not those combinations form potent antigens, except in the case of iodine, but it is hard to explain the sequence of events otherwise.

DR. SULZBERGER.—What Dr. Hopkins has said is correct. There is some proof that many allergens—and perhaps even some of the causal agents of contact-type dermatitis—act as sensitizing agents because they combine with other and larger molecules. They are haptens. This is proved in anaphylaxis. However, recently Landsteiner, and W. Jadassohn and Fierz have found that certain simple chemical substances produce anaphylactic sensitivity and anaphylactic shock without first conjugating with larger molecules—thus definitely proving that, in these instances, it is not the larger molecule, but the conjugate, which is the actively antigenic factor. We may have to revise our ideas about any universality of laws on conjugation of haptens with proteins to form full antigens. Some simple, relatively small molecules can apparently act as full antigens without conjugation.

It is possible that many of the specific properties and immunologic effects which we consider due to protein antigens are really not due to the protein but to constituents or substances of smaller molecular size which accompany the proteins in some way—either in actual conjugation or chemical combination with the protein or simply as accompanying substances adsorbed by the protein. In discussing the chemical and physical nature of allergens, one must, therefore, distinguish sharply between the nature of substances which are able to sensitize and that of substances which are capable of producing reactions in sensitized tissue. In many instances it may require the larger complex to produce sensitivity, while the small molecule is by itself able to elicit specific reactions. I think that is about all I need say at this point. The further discussion of complex antigens, haptens, and allergens which cannot sensitize but which can elicit reactions would take us too far away from the question of contact-type dermatitis.

DR. BENNETT KRAFT, Indianapolis.—Is it possible to sensitize the skin by repeated patch testing so that later the patient will develop a contact dermatitis from materials with which you have patch tested him?

DR. SULZBERGER.—Yes. It is possible to sensitize susceptible individuals with patch tests. And this does occur occasionally, even with the proper technique and the correct concentrations. However, this sensitization is of negligible practical importance if the correct methods are used. For, if one employs the correct concentration and method, the chances that a given subject will be sensitized to a given allergen are about the same as the chances that that patient would become sensitized to that particular agent if he were exposed to it in daily life; in other words, if you use the right technique and the right concentrations and the correct form of application of your test, you will not sensitize a person to paraphenylendiamine who would not have become sensitized to this dye through his ordinary daily exposures. For this reason, when the correct methods and proper technique are used, it is not a practically important danger.

DR. SAMUEL M. PECK, New York.—It is important to realize in our discussion of the role of simple chemicals and sensitizing agents that chemical structure plays an important role in the ability to sensitize. The physical properties of the skin itself are also important. The presence of a thick keratin layer or the fact that the sensitizing chemical is water-soluble is a very important factor in the process of sensitization. For example, in considering chemical structure or activity of the chemical agent, the presence of a double bond in an organic compound will sometimes determine whether you are dealing with a strong or a weak sensitizing chemical. This is very well exemplified in the consideration of dermatitis produced by lactones, such as angelicolactone. You can get practically 100 per cent sensitization with this substance, and it is my opinion that the presence of the double bond in the structure of the active principle is the determining factor for its great activity. Sometimes only one contact with a 100 per cent concentration of angelicolactone will, after ten days and without any further contact, produce sensitization in all areas of the skin. This sensitization is so pronounced that just a 1:1,000 concentration of this substance will elicit a positive patch test.

We can also learn a lesson from this substance in studying the mechanism of the production of contact dermatitis. When we take a previously nonsensitive individual, using angelicolactone, and make a patch test with 5 or 20 per cent of the angelicolactone solution on the skin, we sometimes need as many as 5 applications of this concentration of angelicolactone to the same area of skin before sensitization develops. This is, of course, a demonstration that the concentration of the sensitizing substance is important in the incubation period of the development of sensitization. This point is important in evaluating Dr. Schwartz's discussion. He stressed the fact that, in making patch tests, we must know the threshold which divides elicitation of a sensitization and one which will give us an irritation in all tested individuals. We must remember, then, that if we are testing with active sensitizing substances, it is important not to use too great a concentration of the test substance, lest we develop sensitization in the tested individual.

DR. SULZBERGER.—That is correct. What Dr. Peck said is a very important thing, and one of the things to which I was referring when I said you must use the correct technique in applying patch tests and the correct concentrations. There are certain substances which are such strong allergens that one exposure, even as in a patch test, serves to sensitize almost 100 per cent of individuals exposed.

For example, Rudolf L. Baer, Rostenberg, and I showed that one drop of a 10 per cent solution of 1-2-4 dinitrochlorobenzene (i.e., 0.03 c.c. of a 10 per cent acetone solution of that chemical), dropped on the skin, sensitizes over 50 per cent of all persons. In patch testing one must know all these powerful sensitizing agents and avoid their use. Moreover, one must know the exact concentration and manner in which each substance must be applied before one ventures to apply it. Otherwise, one continually risks various undesirable effects and what may be serious consequences to the patient. For example, while specific sensitization to correct and proper testing is, as I have just said, a rare and negligible occurrence, with improper selection of substances, faulty technique, and wrong concentrations, sensitizations may be produced in a large number of persons and some of these sensitizations may lead to permanent damage. This is of course inexcusable, and the ignorant application of known sensitizing agents or sensitizing concentrations constitutes an error of judgment, if not actual malpractice.

DR. GEORGE H. CURTIS, Cleveland.—I have two questions: First, it is difficult at times to differentiate between a primary irritation and the contact type of eczema due to the volatile irritants such as gasoline, benzene, acetone, and other similar chemicals. I should like to know about any refinements in the technique of testing the skin with these substances in order to differentiate between the two dermatitides.

Second, I have observed contact dermatitis caused by certain substances whose separate ingredients do not give a positive patch test. When this occurs, is it caused by a possible synergistic action of the ingredients or by a possible chemical reaction between the ingredients which forms a new chemical that causes the dermatitis?

DR. SULZBERGER.—Those are two very good questions. The first one is about the technique of testing with benzene and volatile agents of that kind. There are two methods which can, as a rule, be employed. One of them was developed a few years ago by a dermatologist whose name I unfortunately fail to recall. This test consisted of partially filling a test tube with the substance, holding it under the arm, and letting the volatile agent come out and impinge upon the skin. This investigator stated that in this way, and by varying the exposure time, he produced reactions in individuals who were sensitive—provided he first determined the time of the exposure which was necessary to produce reactions in hypersensitive individuals and no reactions in normal skins.

The usual method of testing with certain volatile and potentially, primarily irritating agents, such as gasoline, is to make a dilution of the substance in olive oil or some other oil. From a 20 to 50 per cent solution is the correct one in most instances.

DR. SCHWARTZ.—Dr. Smythe, of the University of Pennsylvania, put it on drop by drop.

DR. SULZBERGER.—As Dr. Schwartz has mentioned, in using new or unknown agents, one must always find out whether or not one is dealing with the primary irritant by seeing what it does to the skins of normal controls.

Many hundreds of substances have now been standardized as to the concentration and mode of application which does not irritate normal skins. If these substances, in the correct concentration and under the conditions of correct patch testing produce an eczematous reaction, one can then conclude that one is dealing with a hypersensitive skin.*

The answer to the second question is yes. That is not an uncommon observation, and it is probably one of the finest ways in which to study synergic effects. One can thus observe the combined effects of agents which potentiate each other's properties in producing allergic reactions. One of the combinations which has been studied most is the combination of mercury and salicylic acid. In my series of several hundred persons, 5 per cent ammoniated mercury and 5 per cent salicylic acid, embodied in petrolatum and applied as patch tests, produce reactions on almost 50 per cent of all persons to whom it is applied; on the other hand, the separate ointments, one consisting of 10 per cent white ammoniated mercury in petrolatum and the other of 10 per cent salicylic acid in petrolatum, both produce reactions in very few of the same test subjects—and apparently only in allergically hypersensitive individuals.

The synergistic and potentiating effect is not caused by a true chemical combination in this instance of synergistic effect of mercury and salicylic acid, for those persons in whom the combined ointment produced reactions were not particularly sensitive to mercury salicylate. One does not know exactly what those synergic effects are based upon, although several possibilities have been considered as meriting and requiring further study.

DR. SCHWARTZ.—I think I can add a little to what Dr. Sulzberger said. If you recall, Dr. Sulzberger told you in his opening address that there are various protective forces and defense mechanisms of the skin, which salicylic acid acts to destroy. Alkalies and acids destroy the keratin of the skin.

DR. SULZBERGER.—I do not think that is the way it works. In some cases, we applied salicylic acid until we macerated the skin with it and then applied the mercurial to this site. Even this did not produce reactions equal to those obtained with the application of mercury and salicylic acid in the same ointment.

I see that many of you gentlemen have requested the floor on this subject, but I think in justice to the other subjects and the other speakers we should dispense with contact-type eczematous dermatitis for the moment and go on to the next subject. Perhaps those who still have questions will have an opportunity to ask their questions at the end of the symposium.

If it is agreeable to all of you I shall now close this subject for the moment, and we shall go on to the second topic, "Allergic Drug Eruptions" by Dr. Adolph B. Loveman, Louisville, Ky.

Allergic Drug Eruptions. ADOLPH B. LOVEMAN, M.D., Louisville, Ky.

In a broad classification of drug eruptions one would naturally have to include all eruptions caused by drugs.

*J. Invest. Dermat. 2: 93, 1939.

This discussion, however, will be limited only to those conditions included in the term, dermatitis medicamentosa. By dermatitis medicamentosa is meant an eruption produced by the absorption and hematogenous spread of a drug or its split product. This absorption may result from inunction, ingestion, injection, or even inhalation. Contact dermatitis which has been so adequately considered by Dr. Sulzberger will not be included in this discussion.

There are very few statistics on the frequency of dermatitis medicamentosa. Sutton, however, feels that the incidence is about 0.3 per cent. In my opinion these statistics seem a little low. There is no drug which has been synthesized or found free in nature to which someone, either now or in the future, will not be known to possess some cutaneous or mucosal hypersensitivity. Unquestionably, as more drugs become available the incidence of dermatitis medicamentosa will increase.

I should like to discuss very briefly the pathogenesis of drug eruptions, as well as both the clinical and experimental evidence for judging the allergic nature of dermatitis medicamentosa.

According to von Pirquet, allergy means an altered reaction of an individual to an allergen, brought about by repeated acquaintance. This so-called altered state can be one of either hypersensitivity or hyposensitivity. Further understanding of any allergic phenomenon implies that there must be an incubation period during which time sensitization develops. As exposures become more frequent, this period usually becomes shorter. The reactions produced by drugs should in no way be related to either the pharmacologic or the toxic action of the drug. Antibodies are not a necessary requisite in judging the allergic nature of a drug exanthema. The eruption, furthermore, should be able to be reproduced by infinitesimal amounts of the drug, so-called specific reaction.

Let us take any drug merely for the purposes of discussion and see how it fits in the above category. Sulfanilamide, only recently introduced, lends itself admirably for demonstration. It is safe to assume, therefore, that no previous contact with this drug has occurred in the past. What happens, then, when such a drug is taken, and sensitization develops? The drug is taken perhaps for a period of from seven to ten days during which time nothing outwardly occurs (incubation period). Then rather suddenly (the patient now having become sensitized) an exanthema of some sort manifests itself. When the drug is discontinued, the eruption usually subsides. When the drug is taken again, however, the incubation period is lessened. Perhaps now only from two to twenty-four hours may elapse before the eruption returns. Occasionally the condition may appear within from ten to fifteen minutes after ingestion of the drug.

It should be emphasized that animals have also played their part in furnishing us with much information on the allergic nature of eruptions. Dr. Sulzberger and Dr. Simon sensitized guinea pigs to arsphenamine, and other men have been able to sensitize these smaller animals to prontosil and phenolphthalein.

I should like to discuss very briefly some fundamental principles underlying all cases of dermatitis medicamentosa. It is important to remember that the same drug may produce different types of eruptions in different persons; for example, phenolphthalein may produce a pemphigoid or bullous eruption in one patient, a scarlatiniform of reaction in another, and a fixed eruption in a third.

The opposite of this is also true. Different drugs may produce a similar eruption in the same person or in different persons, as, for example, arsphenamine, phenolphthalein, aspirin, and luminal may all produce a scarlatiniform type of eruption in either the same or different persons.

The elicitation of the cutaneous response is not necessarily related in any way to the amount of the drug taken. Infinitesimal amounts of the drug may produce a cutaneous response, whereas, occasionally, tremendous doses of the drug may fail to produce an eruption in someone who is known to possess cutaneous hypersensitivity. Unquestionably, however, the extent, character, and intensity of the eruption are related to the size of the dose. A good example may be found in cases of iododerma and bromoderma. In such cases, as more of the drug is taken, the pustules often become more numerous, larger, and take on a fungoid or granulomatous appearance.

Another interesting feature of drug eruptions is that they may appear days, months, or even years after one has taken the drug. This is a well-recognized fact. On the other hand, an eruption may persist months, days, or years after one has discontinued the drug. We have as an excellent example cases of arsenical exfoliated dermatitides.

All drug eruptions, irrespective of their appearance, have many characteristics in common. In the first place, they appear very suddenly. As a rule, they are of a bright red color; they have a symmetrical, although atypical distribution, and usually the course is afebrile. Often they are accompanied by mucous membrane lesions, and, as a rule, the symptoms are very mild as compared with the extent of the eruption.

Even though it has been said that certain drugs produce various types of eruptions and that different drugs produce the same type, nevertheless, we do have some criteria upon which we can base our diagnosis. There are certain drugs which are more or less prone to produce certain morphologic types of eruptions. For example,

luminal, quinine, aspirin, most of the barbiturates, and arsphenamine often produce erythematous types of exanthemas. The so-called "fixed-eruptions" are commonly produced by phenolphthalein, arsphenamine, and have been known to be produced by sulfanilamide, pyramidon, and a few of the barbiturates. Acneform and erythema nodosum-like eruptions are rather frequently produced by iodides and bromides. Recently we had a patient with erythema nodosum which was proved to be caused by sulfanilamide. In addition to the above, we have other drugs which produce pigmentary disturbances and still others responsible for photosensitization, etc.

In conclusion, I should like to emphasize that the dermatologist must limit his field to the skin and the mucous membranes, but the allergist is privileges to delve deeper into the allergic manifestations of drugs. There is no reason why the skin or mucous membrane should be the sole recipients of drug insults. We have all seen recurrent nerve pain due to drugs. I recently saw a patient who had pain in the same tooth following each injection of mapharsen. Agranulocytosis, jaundice, and headache have been observed after the ingestion of certain drugs. I am convinced that many heretofore unknown visceral complaints may also be of drug origin. Certainly after a thorough, but futile, etiological investigation a four-week abstinence from drugs may be worth while in such cases.

DISCUSSION

DR. JOSEPH HARKAVY, New York.—I should like to ask what explanation have you to offer for the persistence of the lesion for weeks or months after contact with a certain drug.

DR. LOVEMAN.—I think that this may be answered, at least to my own satisfaction, in two ways. In the first place, any lesion, regardless of its cause, may persist for an indefinite period; also, inflammatory reactions vary in different patients. Another reason may be that, in many drug exanthemas, the drug is stored, particularly arsenic, and the patient is constantly being resensitized as the drug is being eliminated. This is especially true in cases of bromoderma which often persist for months after the drug has been discontinued. I have seen recurrent attacks of exfoliated dermatitis from arsphenamine two years or more after the original attack. Although in such cases no more arsphenamine had been taken, it is possible that arsphenamine may have been ingested in minute quantities in food or in other medicaments.

DR. ALAN G. CAZORT, Little Rock.—Immunologically, would you consider the drug reaction of which you speak, the reaction to the oil antigens of which Dr. Sulzberger speaks, and the reactions to the water-soluble allergens, the same? If not, in what known ways do they differ?

DR. LOVEMAN.—Perhaps in the general discussion which is to follow, Dr. Sulzberger may have something to say about that. I may mention,

however, that in the eczematous types the reactions are similar both clinically and histologically, whereas in other types the reactions may differ markedly.

DR. SULZBERGER.—I think there is no doubt that many of these reactions are related on the basis of their common cause, a specific sensitization process—in other words, just as they are related to anaphylaxis in that respect or to urticarias in that respect; however, I also think there is no doubt that they are very different in many of their manifestations.

Some of these reactions to drugs are acneform, not eczematous at all; others are productive lesions, sometimes resembling to some degree either carcinomas or sarcomas; and others are fixed eruptions, which have no eczematous component. Different types of reactions to drugs vary in their morphology and pathogenesis. In most of the drug eruptions, other than the eczematous ones, no skin tests are useful. The relationship between the allergic drug eruptions and between the different allergic skin reactions rests simply on the fact that they are all based on specific sensitization.

DR. SAMUEL M. PECK, New York.—In the discussion of drug eruptions we must assume that we are dealing with allergic manifestations, because all of us, I am sure, have seen certain criteria which act as supporting proof for such a phenomenon. It is true that many of the criteria which we have set up to prove that we are dealing with a reaction of hypersensitivity are missing in drug eruptions. The main point in discussing such an eruption as an allergic one is that the patient will develop a skin manifestation which will, first of all, be found only in a small group of individuals; second, very often it will be found after a definite incubation period; and finally, once the eruption has developed, re-elicitation is brought about by the use of a very much smaller amount of antigen than was necessary to produce the original eruption. However, demonstrations of antibodies like the Prausnitz-Küstner antibody and positive patch, scratch, or intradermal tests are missing.

An interesting insight into the mechanism of drug eruptions can be drawn from our experiences with nirvanol eruptions. This drug lends itself very nicely to experimentation, because nearly 100 per cent of the persons who are exposed to this drug develop eruptions.

A group of twenty-five patients with chorea were treated with the original nirvanol which contained equal parts of the levoform and the dextroform. The daily dose was 0.3 gm. It was given from eight to ten days and was discontinued with the appearance of nirvanol symptoms. Twenty-one patients, constituting 84 per cent showed symptoms of nirvanol sickness, and four did not.

During a subsequent period of two years, twenty-eight more patients, most of them having chorea and some epilepsy, were also treated with nirvanol. Twelve were treated with the levoform and sixteen with the dextroform of phenyl-ethyl-hydantoin. At the beginning of our study we did not know whether or not the levo-phenyl-ethyl-hydantoin alone produced the nirvanol sickness. We thought that the dextroform of nirvanol might have only a narcotic effect and that it might not give rise to nirvanol sickness. The daily dose of the levo-nirvanol was then reduced to 0.15 gm. which equaled the amount of levo-nirvanol present when 0.3 gm. of the original nirvanol was given.

We did not want to give double the amount of levo-nirvanol as a single daily dose as this would have increased the intensity of the nirvanol sickness. It was only during the course of our studies that we learned that the dextroform was also able to produce nirvanol sickness, although less frequently in the dose used. The daily dose of 0.15 gm. of levo-phenyl-ethyl-hydantoin, therefore, does not correspond in its sickness-producing power to the 0.3 gm. of the original nirvanol. However, the results were interesting enough.

Whereas the administration of 0.3 gm. of the old nirvanol resulted in sickness in 84 per cent of the cases, seven of the twelve patients treated with a daily dose of from 0.15 to 0.3 gm. of levoform were sick, and no symptoms occurred in the other five. However, in sixteen patients treated with dextro-nirvanol, sickness developed in only five, and eleven remained free from symptoms. We expect to find a higher incidence of nirvanol sickness with an increase in the dose of levo-nirvanol to 0.3 gm. per day. We have been able to show that old nirvanol is a mixture of a levoform and a dextroform of phenyl-ethyl-hydantoin and that levo-phenyl-ethyl-hydantoin is more potent in producing sickness than the dextroform. The experiences with the reelicitation of eruptions in patients who had developed rashes in old nirvanol were not very uniform. In two patients in whom nirvanol sickness was produced by administration of the receiving nirvanol, an eruption developed twenty-four hours after the administration of phenobarbital.

We attempted to produce nirvanol disease in the animal. Over a long period rabbits were given, per os, daily doses of one-third of the subcutaneous lethal dose of the dextro- and levo-nirvanol, respectively. Hemoglobin, erythrocyte count, and body weight showed marked progressive decrease. While the literature lists leucopenia as a characteristic feature in nirvanol poisoning, no regular leucopenia was found in these animals.*

The difference between the dextroform and levoform in their physiologic effects must be due to a difference in either the rate of their reaction with certain cells of the organism or in the rate of their destruction and elimination from the body. The study of brominated homologues might advance our knowledge of the elimination of such drugs.

DR. LOVEMAN.—Before any other questions are raised I should like to emphasize the fact that most of the experimental work in drug allergy has been done on fixed eruptions. I think most of you are well acquainted with this type of reaction.

By a fixed eruption is meant an eruption that recurs in situ with each readministration of the drug. There may be only one isolated spot or there may be many, but each time you give the drug that particular spot which reacted previously will react again, irrespective of the fact that new areas may or may not occur. As these areas disappear, pigmentation may or may not be a sequel.

DR. C. B. BOHNER, Indianapolis.—Am I right in thinking that skin eruptions in children are relatively uncommon?

*Am. J. Dis. Child. 55: 1216, 1933.

DR. LOVEMAN.—I think that is unquestionably true. Drug eruptions due to arsphenamine in children are less frequently encountered than in adults. I have no statistics on other types of eruptions. I should like to hear opinions from some of the pediatricians.

DR. JOSEPH GRINDON, JR., St. Louis.—I should like to ask, is the threshold to other allergens lowered by the development of an allergic drug eruption? It is my opinion that this is true in the eczematous type of drug eruption.

DR. LOVEMAN.—You mean a patient who had dermatitis medicamentosa with a lowered threshold so that he would react to another drug?

DR. GRINDON.—Yes, or food.

DR. LOVEMAN.—I think that is definitely true. Any time the skin is sensitized to one agent, it is often more easily sensitized to other allergens. This is not only true in dermatitis medicamentosa, but is commonly encountered in cases of contact dermatitis.

DR. SULZBERGER.—Dr. Loveman, may I attempt to answer a couple of the questions?

First of all, Dr. Grindon's question. Just as he indicated, one can prove that sensitization to one substance may increase the likelihood to reaction to another substance, for example, in the case of persons getting antisyphilitic drugs. It is not uncommon to find that, after becoming sensitized to arsphenamine and having an arsphenamine dermatitis, an individual who was previously tolerant cannot stand bismuth or mercury. That is a rather common observation. It must be true that sensitization to one thing brings in its train the possibility of reaction to other unrelated substances, and that this holds true in the case of drugs as well as of other allergens.

Now, with reference to the question Dr. Peck has just brought up: I think it is important to point out that he was talking about what is known as a cumulative effect. When continued exposure or continued administration of a substance or drug produces an untoward reaction, which it did not produce previously, is this due to cumulative effect or to sensitization? The reaction can, in most cases of drug eruption, be shown definitely not to be due to cumulative effect. After a drug eruption has once appeared, the minutest amounts of the same drug, even when given years afterward, will usually produce the full picture in sensitive individuals. There is, in the majority of such instances, not the remotest possibility that these reactions are due to amounts of the drug which have remained in the body. Thus, while there is definite evidence of persistent allergy, there is no evidence of a basic role of cumulative effect.

DR. MCKINLEY LONDON, Cleveland.—In view of what has gone before, will you tell me why children who have had infantile eczema for many years do not develop contact dermatitides more regularly or more often than they do?

DR. SULZBERGER.—I think that will be brought up in the discussion of infantile eczemas and atopic dermatitis.

DR. ETHAN ALLEN BROWN, Boston.—Some years ago a test for aspirin sensitivity was discussed in the literature. A grain of aspirin was placed

on the tongue, and the tongue was watched for several minutes for the appearance of a small ridge of mucosa. How reliable is this test? Could it perhaps be of some help in discovering drug sensitivity?

DR. LOVEMAN.—I have had no experience with the particular test to which you refer. I do not believe there is any direct relationship, as a rule, between mucous membrane sensitivity and cutaneous sensitivity. This has been referred to frequently in the literature. In other words, the skin will often react whereas the mucous membrane fails to do so, possessing a more or less selective immunity. If the mucous membrane proves sensitive to a certain allergen, I do not believe we can predict with certainty how the skin will react.

DR. BEDFORD SHELMIRE, Dallas, Texas.—I am definitely convinced that in contact dermatitis sensitization to an external excitant is general, skin and mucous membrane alike being sensitized. The reason for believing the mucous membrane not sensitized is due to faulty patch testing technique.

The patch response to any given antigenic substance depends upon the sensitivity of the individual tested, the thickness of the horny layer of the skin or mucous membrane at the tested site, and the length of time the testing material is left in contact with the tested area. The flexures give a more pronounced patch reaction than the forearms, thighs, or back. Even in ivy-sensitive individuals a positive reaction on a twenty-four-hour test is rarely obtained on the thickened palms and soles.

We carefully dried the tongues and palates of sixteen ivy-sensitive persons and painted these areas with a 1:10 ether extract of poison ivy. Only two showed a reaction on the tongue, whereas all developed erythema or vesiculation of the palate. The bubbles of mucus which rapidly appear on the palate and tongue soon wash away the testing material. The short contact time apparently accounts for the milder reactions in the oral cavity. The thickness of the epithelium of the tongue accounts for the lessened reactions at this site. If the ivy leaf or extract could be held in apposition with the mucous membrane for twenty-four hours as is routinely done on skin testing, patch results would probably be identical.

DR. LOVEMAN.—I do not doubt the accuracy of Dr. Shelmire's experiments. I believe, furthermore, that they will no doubt prove to be a fine contribution to dermatologic literature. I cannot say with certainty whether or not the mucous membrane can be made to react to the same allergen as the skin. I merely state that clinically and actually we rarely see mucous membrane sensitivity. The mucous membrane may possess a selective immunity, or the allergen may be so diluted with saliva as to prevent any reaction. At present that is beside the point, although it is good fertile soil for investigation. The fact remains that we rarely see mucous membrane sensitivity in cases of cutaneous allergy. Jadassohn years ago recorded the fact that, in cases of cutaneous iodoform and mercury sensitivities, although the skin around the genitals would react violently after the application of vaginal tampons, the vaginal mucosa showed no reaction whatsoever. Such cases are not an uncommon clinical experience. Whether or not the mucous membranes could be made to react intentionally is an entirely different problem.

DR. SHELMIRE.—In the attempted preseasonal hyposensitization to plants we routinely employ 1:100 dilution of the specific oleoresin in corn

oil. When this dilution is well mixed with cream, oral reactions are rarely encountered. The saliva and mucus of the oral cavity further act as diluents, and the latter also helps prevent adhesion of the oleoresin to the mucous membrane. Some patients complain of soreness of the mouth and throat, often of such severity that the oils must be further diluted or given in capsules. Some extremely sensitive individuals complain of abdominal cramps. After rather large doses of the specific oleoresins we have not observed perianal dermatitis, which is probably an indication that the oil is absorbed from the intestinal tract.

DR. SULZBERGER.—I think what Dr. Shelmire said is correct so far as it goes. However, it seems to me that there are surely instances of eczematous allergy in which the skin alone is sensitized and the mucous membranes are not sensitized. There are, for example, the exanthemmatous eruptions following the ingestion or the injection of eczematogenous allergens, in which the mucous membranes are not affected. For instance, quinine eruptions occur all over the patient's skin but not on the mucous membranes. In these hematogenous eruptions the sparing of the mucous membranes cannot be due to the fact that the allergen is diluted or washed away at the mucosal surface. There is no doubt, however, that we must somewhat revise our ideas in view of Dr. Shelmire's findings, if he can prove the regular existence of allergic sensitivity to contact allergens, such as poison ivy and plants, in mucous membranes. There can, of course, be no doubt that parts of the mouth will be sensitive and react to ivy extracts if applied in strong enough dilutions. The question is, however, is this capacity of reaction acquired through previous exposure? Is it specific and allergic, like that of the skin? Or is it due to primary irritation or to some other effect? As far as the eczematous type of sensitivity is concerned, and as far as certain eczematous drug eruptions are concerned, there are undoubtedly many cases in which the mucous membranes, when compared with the skin, are relatively resistant to the allergens.

DR. CAZORT.—I should like to know if that could be a chemical reaction.

Allergic Reactions to Plants. BEDFORD SHELMIRE, M.D., Dallas, Texas.

When allergic reactions to plants are discussed, one must consider three more or less distinct clinical types of eruptions caused from contact with three somewhat different types of vegetation, namely, flowers, vegetables, and weeds.

Sensitization to flowers and shrubs has been observed in our office chiefly in housewives and only occasionally in florists. The eruption has usually been confined to the hands, forearms, face, and neck. These have most frequently been of the recurrent, vesicular type, as in most cases sensitization has been extreme and exposure periodic. It should be remembered that in any plant dermatitis, where sensitization of the individual is marked, the resulting dermatitis on exposure is severe and often incapacitating. Exposures are therefore periodic, and the dermatitis is of the recurrent type. The poison ivy plant is the best example of a violent skin sensitizer. Because of the severity

of ivy dermatitis the eruption is a recurrent one, owing to infrequent exposure. Primrose is another good example of a marked skin sensitizer. We have observed, however, acute dermatitis of the severity of an ivy or primrose eruption from such apparently innocuous flowers as the Shasta daisy, chrysanthemum, narcissus, iris, verbena, carnation, zinnia, etc. The milder, chronic types of contact dermatitis from sensitization to flowers and shrubs have been infrequently encountered.

Sensitization to vegetables and fruits has been of both the acute and chronic types. These have been observed in housewives, grocery clerks, and truck gardeners. The eruptions have been almost uniformly confined to the hands. The majority of our patients have been housewives, and frequent washing of the hands by these persons probably accounts for the localization of the eruption on these areas, as washing diminishes the possibility of manually transferring the antigenic oleoresins to other portions of the body. We have observed contact dermatitis from such common vegetables and fruits as spinach, tomatoes, radishes, mustard greens, corn, Irish potatoes, water cress, carrots, oranges, lemons, grapes, etc.

Dermatitis from contact with weeds presents an entirely different clinical picture. The eruption usually involves all the exposed areas—face, neck, hands, forearms, ankles, and legs. In long-standing cases only the abdomen and back are spared. Sensitization to weeds is usually not so marked; therefore, erythema, pruritus, and subsequent thickening of the affected areas are the rule. Vesiculation and swelling are only rarely encountered. Lichenification of the flexures is an outstanding characteristic of weed eczemas. The eruption is at first seasonally recurrent, beginning in the spring or early summer and lasting until after the first frost or freeze. The dermatitis often recurs during the growing season of plants for many years, but eventually it becomes perennial. The skin becomes so thickened from the constant trauma of rubbing and scratching that only a moderate remission occurs during the winter months. The former severity recurs when the new spring weeds appear. Clinically these chronic cases closely resemble generalized neurodermatitis or atopic eczema.

Those usually affected are farmers and farmwives, oil field workers, members of surveyor and construction gangs, etc. As weeds grow profusely in cities in waste places, vacant lots, and along sidewalks, few persons escape all contact with this type of vegetation. When skin testing with weeds we routinely test with tobacco, extracts of pyrethrum flowers, derris, cube, timbo, and barbasco roots, the latter being common constituents of insect sprays and powders which are frequently used by farmers for stock sprays and insect repellents.

Weed-sensitive individuals resemble hay fever and asthma victims and present a polyvalent sensitivity. A person may be found sensitive to only one weed, but it is more usual to find sensitivity, in varying degrees, to half a dozen or more different species of weeds. The more oleoresins used in testing, the more numerous are the skin reactions. Some responses of course are group reactions. Nevertheless a weed-sensitive individual should be tested to all the common weeds in his environment.

Because of the limited time, my subsequent remarks shall be confined to methods of patch testing in suspected cases of weed dermatitis. The fresh leaf, portions of the dried plant, and the extracted oleoresin may be used for the testing material. As most weed-sensitive patients come from rural communities and often must travel a considerable distance to the specialist's office, patch testing to determine the offending plants is usually necessary on the patient's initial visit. This requires frequent trips during office hours into the country to collect plants which the patient is most likely to contact. Weeds common to his particular environment often grow sparsely or only in certain parts of the physician's locality. This necessitates rather wide excursions for the collection of a few common specimens. After the plants are collected the application of the patch tests with the necessary washing of hands after each test requires more time than can be devoted conveniently to one patient. Because of the time element, when tests are done with fresh specimens, the testing is always incomplete. Also, many plant leaves act as irritants on twenty-four-hour tests, and controls must be done.

Plants may be collected, completely dried, ground to a meal, and stored for patch testing. With the plant testing material available, even when one works rapidly, it requires an hour or more to apply the meal of some 60 plants, the number used by us in routine patch testing. Plant meals rarely act as irritants. It requires a large amount of adhesive tape to hold the meal in contact with the skin, and adhesive dermatitis is not infrequently an annoying complication.

Plant oleoresins may be readily extracted with ether and dilutions of this crude extract used for the testing material. When properly prepared these oleoresins are relatively stable. By using the uncovered patch method, some 60 tests can be applied in about five minutes. The same method is employed in testing persons to garden vegetables, fruits, flowers, and shrubs.

Mature, green plants are collected and thoroughly dried in the shade to preserve the chlorophyll, which is useful as a coloring agent to delineate the patch site. After thorough drying, the plants are broken or ground and loosely packed in a fruit jar and covered with ether.

The jar is sealed to prevent evaporation. The ether-covered plant is allowed to stand for twenty-four hours. The ether containing the dissolved plant resin is filtered and then placed in an open vessel to allow evaporation. When evaporation has proceeded to the point where a thick, resinous, greenish residue is left, nine parts of acetone are added to give a 1:10 dilution of the crude resin. We have now tested some 600 individuals (36,000 tests). This dilution of the crude resin, as prepared above, does not act as an irritant but evokes positive skin reactions in sensitive individuals.

We have purposely made no attempt to purify these crude resins, believing that the cruder the extract, the more closely it resembles the plant oil contacted in nature. If plants are collected during the dormant state, when chlorophyll is lacking, the resulting extract is golden yellow to brown in color. Present evidence indicates that young immature plants do not contain as much of the dermatitis-producing oleoresins as do the mature plants.

The 1:10 dilutions of the crude plant oleoresins in acetone are placed in 4 c.c. cork-stoppered vials. An oversized cork is preferable. Applications are made with the slightly moistened end of the cork. Only enough testing material should be placed on the skin to leave a faint greenish tinge at the contacted site on evaporation of the acetone, which is almost immediate if a thin film is applied. Tests are placed on the back in vertical rows of ten, three rows on each side of the spinal column. Patch sites are not covered. Patients are warned not to scratch uncovered reacting areas as small amounts of antigenic oleoresins may be transferred manually to other parts of the body. Lines drawn between the vertical and horizontal rows of tests with an indelible pencil divide the back into small squares and aid in identifying the patch sites. If test sites are covered, dilutions should be reduced to 1:20 or higher, since the testing material is held in contact with the skin for a longer period.

Our best results of treatment have been in persons who have avoided further contact with weeds. In most instances this has been impossible without a complete change of occupation. After thorough trial, attempted hyposensitization by the intramuscular injection of the antigenic oils has been abandoned, owing to the poor results obtained. This failure was probably due to the difficulty in graduating the dosage and in having the patient return for the large number of injections which are usually necessary to even moderately reduce the sensitivity. The three- and four-injection method advocated for poison ivy has been found absolutely worthless in our office for both ivy and weed dermatitis alike.

If statements of patients and the absence or diminution of the seasonal eruption can be taken as evidence of hyposensitization, then

oral treatment of the weed-sensitive patient offers some hope. Such treatment is started several months before the spring weeds appear and is continued through the growing season of the plants. Patients are given a small quantity of the antigenic oils in a dropper bottle, diluted to 1:100 with mazola. They are instructed to take 1 drop daily and increase the dose gradually until 5 or 10 drops are ingested once or twice daily. If symptoms such a flushing, urticaria, abdominal cramps, etc., develop, the dosage is immediately reduced. The drops should be taken through a straw after meals, well diluted in cream, or in gelatin capsules. Further trial may prove larger dosage necessary. Oleoresins of weeds proved nonpoisonous have now been given in doses as high as 50 drops daily.

Some plant oleoresins, such as the crotons, are intestinal irritants. The entire plant or the roots and berries of many plants—Jimson weed, partridge pea, cowbane, locoweed, snow-on-the-mountain, pokeweed, black nightshade, and certain species of cocklebur—are poisonous if eaten. Since the toxicity of all plant oleoresins is not known, we routinely advocate one drop of the 1:100 dilution of any weed oleoresin as an initial dose.

The 1:100 dilution of the oleoresins is readily prepared by placing 24 drops of the stock 1:10 testing material in a half-ounce dropper bottle. The bottle is then filled with mazola and thoroughly agitated. If such therapy is attempted during the presence of the eruption, as small a dose as 2 or 3 drops will often cause an increase in pruritus and not infrequently a generalized urticaria. These same individuals can frequently tolerate a large number of drops if taken preseasonally.

To date we have no proof that a patient can be hyposensitized to weeds by the ingestion of the antigenic oleoresins. We do have actual proof, however, that the patients treated by this method feel that they have either been desensitized or markedly benefited by such therapy. They return or write in regularly for a refill of their bottles which have to date been dispensed free of charge since this has been entirely an experimental problem. Our difficulty in these patients has been to prove that they still contact the offending weed.

DISCUSSION

DR. ALAN G. CAZORT, Little Rock.—I am interested in *Helenium*. Last summer only 3 of 60 allergists mentioned *Helenium tenuifolium*, or bitterweed. I should like to know what the distribution of that plant is and how important you consider it as a cause of contact dermatitis.

DR. SHELMIRE.—We had hoped that, if an individual was sensitive to any species of a genus of a plant family, skin sensitivity could be detected by patch testing with an extract of any species of that plant genus. For example, of the several species of *Helenium* growing in Texas, two species are locally common—*Helenium microcephalum*

(sneezeweed) and *Helenium tenuifolium* (bitterweed). Both are marked skin sensitizers. Sensitized individuals usually give equal patch reactions to both species. Since *Helenium* is generally distributed and locally common over the whole United States, it would be very convenient to use one extract for the entire group. This may be found possible. Unfortunately, such group testing does not apply to other important weed genera. The giant ragweed is a very weak skin sensitizer, and a patient is rarely found sensitive to this plant. The three other species of ragweed with which we have worked, namely, short, western, and southern ragweeds, seem almost identical in skin reactions. Therefore, if one used an extract of giant ragweed for routine patch testing, he would fail to diagnose practically all of the ragweed-sensitive cases. The same can be said of the *Iva* (marsh elder) genus. Narrow-leaved and burweed marsh elders are both marked skin sensitizers. *Iva ciliata* (rough marsh elder) must be a very weak skin sensitizer, as we have never encountered a positive patch reaction with the fresh leaf, ground meal, or extracted oleoresin of this plant. Individuals extremely sensitive to other species of marsh elder routinely give negative patch reactions to *Iva ciliata*. For the present, we must conclude that the oleoresins of plants are much more specific than the pollens (water-soluble fraction of hay fever).

DR. I. S. KAHN, San Antonio.—What part of the *Parthenium* do you use, the flowers or the leaves?

DR. SHELMIRE.—When extracting oleoresins from weeds and flowers we use all portions of the plant which grow above the ground. Such plants are usually cut just above the roots. When extracting vegetables we use all portions touched by man, such as leaves, stems, fruit, and roots. We utilize only the leaves of such vegetables as lettuce, spinach, cabbage, etc. When extracting such vegetables as carrots, beets, potatoes, etc., all portions of the plant are used. We have recently seen a housewife sensitive to carrots. Patch tests with the carrot root gave markedly positive skin reactions, while tests with the crushed leaves and stems were negative.

Mature plants should be used for extracting purposes, for such plants apparently contain much more oleoresin than young plants. The greater severity of contact dermatitis during the pollinating season of plants is apparently due to the greater oleoresin content of plants at this period. Pollens seem to play a minor role in the causation of contact dermatitis. The pollens of some plants, such as poison ivy, do not contain the dermatitis-producing oleoresin. There are no resin ducts in the outer portions of the stamens and in the anthers of the poison ivy flower. The pollen, therefore, could contain no resin. We collected poison ivy (*Toxicodendron radicans*) pollen this spring. Ivy-sensitive persons routinely gave negative tests to this pollen. The pollens of other plants, such as ragweed, parthenium, etc., contain much less of the dermatitis-producing fraction than the leaf. This can best be demonstrated on a mildly sensitive patient on whom patch tests with the leaf give a moderately positive skin response, whereas the pollen will often give an absolutely negative reaction.

DR. CHARLES A. SPIVACKE, New York.—In New York florists' shops, in the chrysanthemum season when they use so many varieties that bloom, pompons, etc., I find that some of the workers get marked contact

dermatitis from those flowers. I have applied patch tests which have shown very marked reactions to the flower, the leaf, and the stem, and I should like to ask whether or not, as you explained before, you can desensitize some of these plant cases, including chrysanthemums, with injection or by oral administration.

DR. SHELMIRE.—I was misunderstood if you thought I said "desensitize." For the present, we should use the term "hyposensitize." Our attempts to reduce the sensitivity of a patient through the intradermal and intramuscular injection of small quantities of the antigenic oleoresins has consistently met with failure. This failure may be due to the fact that patients could not be induced to return regularly for the required number of treatments, although some received thirty or more injections.

When a person was found sensitive to a plant through patch testing with the 1:10 fat solvent extract by the uncovered method, he was then retested by the covered twenty-four-hour patch method with serial dilutions of 1:100 to 1:100,000 of the antigenic oleoresins in corn oil. In attempted hyposensitization our initial injection was 0.1 c.c. intramuscularly of that dilution which failed to give a cutaneous response. The dosage was gradually increased unless systemic symptoms developed. Extreme care is necessary when treatment is given coseasonally, as the addition of a few tenths of a cubic centimeter of a dilution as high as 1:100,000 is frequently followed by a focal flare-up of the eruption (urticarial) and often by generalized urticaria. Gastric pains, diarrhea, and a general flushing are not uncommon with the larger doses. At the present time we are relying entirely on the oral method in attempted hyposensitization. Our chief complications to date have been dermatitis of the lips and erythema and soreness of the mouth. Both of these can be avoided by taking the drops through a straw, well diluted with cream, or in capsules. A No. 1 capsule holds approximately 16 drops. The patient places the required number of drops from the dropper bottle into the capsules immediately before ingestion.

DR. SULZBERGER.—Dr. Spivacke, one of the best cases of specific desensitization I myself have seen was a chrysanthemum case. The florist, who had his exposures every year in the fall at the chrysanthemum season, was affected each year until he got his specific injections. In following years he had no trouble at all, despite his remaining at the same sort of work with the same degrees of exposure to the same sort of chrysanthemums.

DR. G. V. STRYKER, St. Louis.—I should like to ask Dr. Shelmire about his technique for gathering specimens. Does he select the whole plant or only certain parts? Does he permit the plant to dry, or does he immediately put it into the jar in which it is to be extracted?

In working with a group of cases of industrial dermatitis in jonquil growers in St. Louis, I found that a large number of the people who grew the jonquils, cut the flowers, and handled the bulb were sensitive to patch tests. In these highly sensitive individuals, when I used pollen, the leaf, or the stem (if the stem was unbroken and if I was careful to keep the sap which runs out away from the skin), patch tests were positive.

That same variety of jonquil which produced a violent dermatitis shortly after it had been cut would not affect the skin of a sensitized

individual if the jonquil had been transferred into water, taken to the wholesalers, and then delivered to the florists, remaining in water over a period of from twenty-four to forty-eight hours. Apparently the activating substance or sensitizer had been drained out or diluted and was no longer a sensitizer.

It is rare for retail florists or consumers to develop the dermatitis which is so common among the growers.

DR. SHELMIRE.—Plants should be thoroughly dried before extracting their oils with ether or acetone. Oleoresins deteriorate rather rapidly in the presence of moisture. Many plant oleoresins are soluble in water. At least the dermatitis-producing fraction is water-soluble, since fresh-water extracts will give positive patch reactions. Such water extracts kept for more than thirty days will rarely give positive cutaneous responses even in highly sensitive patients. Ether or acetone extracts of plants, if water-free, are relatively stable; some of our extracts, now over 4 years old, still evoke positive skin reactions.

We speak of the dermatitis-producing fraction of plants as oleoresins, yet oleoresins are not considered water-soluble. Many patients state that contact with a plant wet with dew or rain will cause a much more severe dermatitis than contact with a dry plant. This is apparently true of many plants such as *Iva angustifolia*, *Helenium microcephalum*, parthenium, short ragweed, etc., since their oleoresins are soluble in water. The oleoresins of other plants, such as poison ivy, are absolutely water-insoluble. We have never succeeded in getting a positive patch test with a water extract of this plant.

The leaves of many herbs, notably poison ivy, contain no resin ducts in their epidermis so that the leaf must be bruised when doing a patch test. In other plants the oils appear as tiny droplets on the surface of the leaves. As a routine procedure, all leaves should be bruised before patch testing. A twenty-four-hour covered patch test with a plant leaf is not an accurate test. A patient never has continuous contact with a plant for twenty-four hours. To test ordinary clinical sensitivity to a plant we believe that a one-hour test with the crushed leaf is the most accurate. We have now tested the leaves of some seventy-five weeds. Approximately 25 per cent give irritative reactions on at least some noneczematous subjects on twenty-four-hour test. Therefore, when tests are made with fresh leaves, controls should always be done on several subjects.

I cannot explain the cases cited by Dr. Stryker, unless those cutting the jonquils were coming in contact with the fresh tissue juices of the plant, and the reactions were irritative and not allergic. I have tested the juice or sap of some 500 Texas weeds. The milky juice of poison ivy is a marked escharotic for man and animal. The milky juice of many members of the spurge family cause a constant follicular papulopustular irritative reaction. The juices of many buttercups, especially the *Ranunculus sceleratus* or ditch crowfoot, are rather marked skin irritants.

DR. C. MALONE STROUD, St. Louis.—I am glad to see some converts to the idea that hyposensitization with plant oils can be effected. Pertinent to the remarks of Dr. Shelmire regarding concentration of plant oils, I wish to speak briefly of some experiments which Dr. Martin Engman, Jr., and I did a few years ago with mustard oil.

By the application of serial dilutions of mustard oil we tried to determine the threshold of irritability in the skins of people with various ailments. We found that it varied considerably, not only in various skin conditions, but from day to day in the same individual. It seems to me that it is as important to determine the threshold of irritability to general irritants as to determine the threshold of concentration with specific offenders.

These experiments led me always to use a method of control in testing for specific offenders when the suspected agent is a known irritant. For instance, turpentine in sufficient concentration will irritate all human skin. It may act as a specific allergenic reactor.

Thus, in testing with turpentine, a piece of gauze 1 cm. square, saturated with turpentine, is applied to the skin of the suspected individual. A similarly treated piece of gauze is placed on the skin of a normal individual at the same time. If the turpentine reacts as a specific etiological agent, the reaction of erythema and itching will appear much more quickly than in the normal individual, and there will be an exacerbation of the original lesion.

DR. SULZBERGER.—Dr. Stroud said that one must determine in advance whether or not a patient has an irritable skin; and that one must find out whether or not the substance used in testing is producing an irritation because the particular patient's skin is, in general, irritable, as well as whether or not the substance produces an irritation because of its general irritating properties. He has made it a practice to apply a suspected substance to his own skin as well as to the skin of the patient he suspects of being sensitive or easily irritated; and he then compares the length of time it takes for the reaction to appear on his own skin and on that of the patient. If the patient reacts much sooner than he does, he concludes that the patient either has an irritable skin or is sensitive to the substance. Is that right?

DR. STROUD.—Yes.

DR. SULZBERGER.—And he asks me to say what is wrong with that picture. As far as I can tell from his description, he is simply employing an unusual method in the attempt to find out, first, whether or not a substance is a primary irritant; and, second, whether or not a patient has a generally irritable skin. Both of these points must, of course, be elucidated, but I cannot decide whether or not Dr. Stroud's advice is as good as the usual orthodox methods.

DR. SHELMIRE.—The reaction at a given site depends upon the sensitivity of the patient and the length of time the specific antigenic substance is left in contact with the skin. Sites of previous dermatitis are much more sensitive than formerly unaffected areas. By using subreactive dilutions of plant oils we have been able to flare-up patch sites which have been healed for months, although the surrounding previously unaffected skin showed no reaction to the same dilution. In a patient of given sensitivity, patch reactions to a given antigenic agent vary according to the thickness of the horny layer of the skin at the tested site. The flexures show the greatest response. Patch tests on the palms and soles are usually negative, even in extremely

sensitive individuals. Skin of the back, abdomen, arms, and thighs reacts about the same if these areas have not been affected recently with a dermatitis.

Further work needs to be done on the latent period of patch tests —that is, the time interval between the application of the test and the appearance of the reaction. As a general rule, the shorter the latent period, the more intense the cutaneous response. However, this is not an infallible rule.

During the testing of a large number of persons with the 1:10 dilution of poison ivy extract, we encountered many who did not react until the fourth, fifth, sixth, or even seventh day. By repeating the patch tests with the same dilution, the latent period could frequently be reduced to twenty-four hours without appreciably increasing the severity of the cutaneous response. The time interval was shortened, but the cutaneous reaction was not increased. I am not familiar with the time tests referred to.

(Symposium to be continued in the next issue)

THE AMERICAN SOCIETY FOR THE STUDY OF ALLERGY

St. Louis, Mo., May 15, 16, 1939

Electrolyte and Water Exchange in Bronchial Asthma. A. V. Stoesser, M.D., and M. M. Cook, M.D., Minneapolis, Minn. (Abstract.)

Investigation of the possible relationship between electrolyte and water metabolism and the asthmatic state was suggested by the clinical observation of an uncontrollable asthma patient whose symptoms were severely aggravated by a high sodium chloride intake. Twelve patients were studied who had proved intractable under routine allergic management. Various procedures affecting the electrolyte and water metabolism gave results as outlined below:

1. Artificial fever gave only transient benefit in asthmatics whose sodium chloride intake was normal or high before and during treatment.

2. Artificial fever gave striking improvement or complete remissions in asthmatics on a continuous special low salt diet (below 120 to 200 mg. of Na daily).

3. Remissions from the low salt intake plus artificial fever could be terminated promptly by adding 1 to 2 gm. of NaCl to the diet (all other factors remaining the same).

4. Potassium chloride (6 to 10 gm. daily) when added to the special low salt diet caused cessation of asthma in milder cases. In more severe cases asthma continued while KCl was taken, but ceased at once when KCl was discontinued.

5. Potassium chloride (6 to 10 gm. daily) given to patients during remissions did not cause recurrences of asthma.

The foregoing observations suggested that depletion of body water and salt (NaCl) tended to favor remission of asthmatic symptoms. In

order to study the effect of increased body hydration separately, without corresponding increase in body salt, six asthmatic patients on low salt diets were subjected to a posterior pituitary (pitressin) antidiuresis sufficient to cause the storage of 1 to 2 kg. of extra body water without storage of extra body salt.

6. In repeated experiments all but one patient showed no aggravation of asthma in spite of excessive pitressin hydration, and over half of them experienced complete remissions during hydration.

7. In all cases improvement or complete remission was evident by the end of the diuresis period which followed withdrawal of pitressin.

It would appear from the foregoing observations that the sodium, potassium, and water metabolism bear an important relationship to the asthmatic state. It is suggested that drastic salt depletion favors a reduction of asthmatic symptoms. Biochemical and metabolic balance studies now in progress are expected to afford further information on the physiologic mechanism involved.

No positive therapeutic implications are warranted at this juncture, as these procedures are rather involved and technically difficult to carry out with effective exactness. Hence, the whole subject is of more value as an investigative tool than as a therapeutic procedure.

DISCUSSION

For discussion of this paper, see page 14.

THE AMERICAN SOCIETY FOR THE STUDY OF ALLERGY

Resolution

WHEREAS, the American Society for the Study of Allergy has learned with deep regret of the death of Dr. John A. Murphy, and

WHEREAS, the Society has suffered the loss of one of its most beloved and devoted members, and

WHEREAS, his character, patience, and consideration for others were admired by all who knew him and to them his death is a great personal loss, and

WHEREAS, his ability in the field of allergy has long been recognized and his contributions to the literature have helped materially to advance this branch of medicine, be it therefore

Resolved, That we, The American Society for the Study of Allergy, formally and sincerely record our great loss and misfortune in his passing, and be it further

Resolved, That a copy of these resolutions be spread upon the minutes of the Society, that a copy be forwarded to his wife and family, and that a notice be printed in the official journal of the society.

H. B. WILMER
MERLE M. MILLER
LOUIS TUFT

Annual Review

SERUM ALLERGY*

MAX HARTEN, M.D., AND MATTHEW WALZER, M.D.
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THE increasing frequency with which animal sera are being employed in therapeutics today is accentuating the importance of the allergic aspects of the subject.

The manifestations of serum allergy are varied and are undoubtedly based upon a variety of mechanisms, the nature of which is subject to considerable dispute. The subject is too large to be adequately presented in a review of this kind. It will be our purpose to present only the most important of the more recent contributions and to attempt to evaluate their significance.†

With the nature of the involved immunologic mechanisms so much in doubt any attempt at exact classification of the various manifestations of serum hypersensitiveness meets with failure. To facilitate the presentation of the subject, however, advantage will be taken of the few distinctive clinical characteristics and of the little available immunologic information to assay a rough grouping of the various types of serum reactions.

Most of the available data deal with allergy to horse serum. Hence, any reference to serum in the following pages applies to horse serum unless otherwise specified.

It is most convenient to separate that form of serum allergy which occurs typically after an incubation period—characteristically of at least several days' duration—from those which occur immediately or within a few hours after serum administration. The former, known as serum-sickness or serum disease, also presents certain symptomatic differences which aid in differentiating it from the more immediate type of serum reactions. These will be discussed under the various headings.

I. SERUM-SICKNESS

A. TYPICAL SERUM-SICKNESS

1. *Immunologic Aspects: a. Antibodies and the Mechanism of Serum-Sickness.*—Several types of antibodies have been reported in relation to serum-sickness. They include precipitins (anaphylactic antibodies), heterophile antibodies, and atopic reagins. Little has been contributed in the recent literature to add to our knowledge of the precipitin and reagin in relation to serum-sickness. Briefly, it may be stated that

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†For a more complete critical analysis of the earlier work on serum allergy, the reader is referred to the excellent reviews on this subject by Coca.[1, 2]

precipitins (or anaphylactic antibodies) are frequently found in the blood of human beings following the administration of immune animal serum. It is important to remember that such precipitins may occur without the development of serum-disease.[1] Furthermore, they are regularly absent in the blood of patients treated with normal horse serum, even in the presence of typical serum-sickness.[2, 3]

Atopic reagins occur frequently, but by no means regularly, following the administration of therapeutic horse serum. They may appear in the blood late in the course of serum-sickness and persist for a period of time varying from a few days to a few weeks.[104]

Heterophile antibodies in relation to serum-sickness have received some attention in the recent literature. Davidsohn[4] found an increase in heterophile antibodies (hemolysins and agglutinins for sheep red blood cells) in the blood of patients treated with normal or immune horse serum. Increase of the agglutinins was found to occur more regularly than the increase of the hemolysins. These antibodies usually appeared prior to the onset of serum-sickness. As in the case of precipitins, heterophile antibodies occasionally occurred without the development of serum-sickness. Davidsohn, nevertheless, believes that a high titer of heterophile antibodies in human blood may be considered to be indicative of a recent episode of serum-sickness. It has been demonstrated by Powell,[5] however, that the removal of heterophile antigen from immune horse serum does not prevent the development of serum-sickness in patients receiving such serum. This finding casts further doubt upon the etiological significance of heterophile antibodies in the causation of serum-sickness.

Report of another change in circulating antibody associated with serum-disease was recently published by Davidsohn.[9] He reported a definite elevation of isoagglutinins in many patients with serum-sickness following the administration of horse serum. The increase was most marked in the "A" (anti-B agglutinins) and was less pronounced in the "B" (anti-A agglutinins). Patients who did not develop serum-sickness showed only slight elevation in isoagglutinin titers.

An analysis of all the available data still fails to reveal a constant association of any type of antibody with serum-sickness. One is compelled to conclude that the mechanism of serum-sickness cannot be correlated with any of the antibodies which have thus far been detected in this condition. In fact, the doubt expressed by Coca[2] that any circulating antibody is responsible in the causation of serum-sickness still seems justified.

The recent contributions by Voss[10a, 10b] and Szirmai[11] dealing with the mechanism of serum-sickness have attracted considerable attention and comment and will therefore be analyzed in detail.

Encouraged by the favorable reports resulting from the use of autohemotherapy in the treatment of serum-sickness, Voss[10a, 10b] studied

the prophylactic and curative effects on serum-sickness of convalescent serum obtained from patients with this illness. This in time led him into studies on the immunologic nature of serum-disease. All of his experiments were performed on children. From 1 to 10 c.c. of convalescent serum were injected intravenously into children who had received immune horse serum. Injections were given from the first to the seventh day after the administration of antitoxin. In others the injections of convalescent serum were delayed until early or late in the course of serum-sickness. The injection of 1 c.c. of convalescent serum on the day following the intramuscular injection of diphtheria antitoxin resulted in a local urticaria at the site of the horse serum injection. This started within three minutes, reached its height (3 to 4 inches in diameter) within one-half hour, and began to fade after a few hours. The reinjection of 4 c.c. of the same convalescent serum on the following day produced the same result but to a milder degree. No further reactions could be elicited with subsequent doses of convalescent serum, even when larger amounts were injected. When the convalescent serum was injected on the second or third day after the antitoxin administration, local reactions of stronger intensity were obtained. In none of these cases, however, were any reactions of a constitutional nature noted. The intravenous injection of 5 c.c. of convalescent serum on the fourth day was followed within a few minutes by an urticaria starting at the antitoxin site and gradually spreading over the entire body. It disappeared within twenty-four hours. A reinjection of convalescent serum the following day produced no local or general reaction. The injection of convalescent serum in another child in whom serum-sickness had already started resulted in the rapid aggravation of serum-sickness, including edema of the eyelid, lip, and glottis, backache, headache, vertigo, rise in temperature, together with "shocklike" symptoms (vomiting, lowered blood pressure, difficulty in breathing, etc.). The acute symptoms subsided in three hours, but the urticaria persisted until the following day. Between the fourth day and the onset of serum-sickness, the injection of convalescent serum produced symptoms of increasing severity.

The convalescent sera used in the above experiments were usually drawn on the eighth day after the subsidence of symptoms of serum-sickness. They were found to be equally effective when taken fourteen days and four weeks after the end of the serum-sickness. These sera, when stored in the icebox with the addition of phenol as a preservative, lost their activity in from three to six months.

Sera obtained from children who had received immune horse serum but had failed to develop frank symptoms of serum-sickness were not entirely impotent. The intravenous injection of such sera usually produced delayed (local?) reactions. Occasionally, mild immediate

reactions resulted, and in a few instances no reactions developed, even when large doses of serum were administered.

Voss explained the above phenomena in the following manner. He assumed that the injection of convalescent serum increased the titer of antibodies in the treated person to the concentration necessary for the production of serum-sickness, according to the theory of von Pirquet and Schick. However, the presence of antibodies in the convalescent sera used by Voss is purely an assumption since no antibody studies on these sera were reported.

Voss attempted to obtain further information on the nature of serum-disease in another series of experiments with a slightly modified technique.[10c] In these, he again employed an inverse technique for the local production of wheals, the convalescent serum being used as the immune serum. Cutaneous sites were prepared by the intracutaneous injection of 0.1 c.c. of horse serum in normal (?) subjects. From two to eight hours later 1 c.c. of convalescent serum ("antiserum") was injected intravenously. A large wheal (3 to 4 inches in diameter) soon developed and reached its height within thirty minutes. The reaction could be obtained even when a 1:100,000 dilution of horse serum was used for the intracutaneous injection. Cutaneous sites prepared by the injection of either sheep or bovine serum also reacted following the intravenous injection of convalescent serum obtained from horse-serum-treated cases. Not only the local phenomenon but also "serum-sickness" could be produced in patients treated with normal (?) bovine or sheep serum and injected with from 1 to 10 c.c. of convalescent serum obtained from subjects of serum-sickness who had received immune horse serum. These findings cannot be considered indicative of a lack of specificity in the reactions obtained by Voss in view of the available evidence that many mammalian sera contain a common antigenic principle.[12]

Further work along the lines of Voss's experiments was carried on by Szirmai.[11] His studies were primarily directed at the reproduction of the local cutaneous phenomenon described by Voss. Twenty convalescent sera were studied. These were obtained from three to fourteen days after the subsidence of serum-sickness from patients treated with immune horse serum. At least three subjects were injected intracutaneously with each of these sera. The amount and dilution of serum used were not stated. After eight hours, from 1 to 5 c.c. of convalescent serum were injected intravenously. Szirmai reported an inconstancy of results on different subjects. One convalescent serum, for example, produced a negative result in one subject, a delayed local reaction in another, and an immediate local reaction in a third. From this he justly concluded that one must take into consideration not only the effects of the convalescent serum but also the role played by the

subject of the experiment in the production of the phenomenon. Moreover, Szirmai reported that most of the sera obtained from patients, who failed to develop serum-sickness after therapeutic injections of immune horse serum, were also able to produce the inverse local phenomenon. Conversely, not all of the convalescent sera obtained from subjects of serum-sickness could produce the inverse reaction.

Szirmai's studies, therefore, raise considerable question as to the theoretical significance of Voss's experiments. An absence of protocols and a lack of information as to technical details in the papers of both workers seriously handicap any attempt at critical analysis of the above experiments. Despite these limitations, however, several impressions may be gained from this work. It appears to add additional confirmation to the existent knowledge that, during and following serum-disease induced by the injection of immune animal serum, circulating antibodies may be found in the blood. These antibodies vary quantitatively and qualitatively in different cases. Some of them have the power of reacting with the antigen in the human skin. New evidence that any particular antibody is responsible for the development of serum-sickness has not been given.

In analyzing the above experiments several other points should be kept in mind. A cautious interpretation is needed in evaluating attempts at the artificial production of serum-sickness. It is not sufficient to consider urticaria as the single and adequate criterion of the syndrome of serum-sickness. It is common knowledge that the cutaneous wheal may be reproduced by many mechanisms, specific and nonspecific. It is therefore hazardous to interpret a wheal or even a generalized urticaria as a perfect reproduction of the syndrome which the clinician has come to recognize as serum-sickness.[13]

Another important consideration in interpreting these experiments is the fact that the intravenous injection of convalescent serum into patients who had received immune horse serum intramuscularly could not induce "serum-disease" on the first three days. If Voss's assumption that the convalescent serum contained the antibody responsible for serum-sickness were justified, it should have been possible to induce a generalized serum sickness with injections of convalescent serum at any time after the injection of the horse serum.

Attempts to understand the mechanism of serum-sickness are further complicated by recurrent reports[14] of serum-disease resulting from injections of human serum. Because of the marked increase in the use of blood transfusions and human convalescent sera in therapeutics, the extreme rarity of such reports (less than a dozen) necessitates a conservative attitude in the interpretation of these reactions. As has been pointed out, drug allergy may at times closely simulate the picture of serum disease[13, 2] and may be mistaken for it. No better example of this fact can be offered than the syndrome not infrequently

encountered following the use of sulfanilamide. In this connection, Hageman and Blake[15] have suggested the term "drug fever" for this syndrome and have pointed out its remarkable similarity to serum-sickness from the point of view of incubation period and symptomatology.

Foshay and Hagebusch[16] have suggested "that the major phenomena of serum-sickness are due to a release of histamine or a histamine-like substance in the tissues and into the circulation consequent on the union of serum protein antigen and antibodies." Acting on this premise, they administered histaminase in an attempt to control and prevent symptoms. Although favorable results were reported, the authors admitted that they could not establish the validity of their hypothesis merely on the basis of the good result obtained with their treatment. Granting the role of histamine in causing the symptoms in serum disease, its presence does not necessarily establish an antigen-antibody reaction as the mechanism producing it.

In the absence of any adequate explanation for the mechanism of serum-sickness on the basis of an antigen-antibody reaction, one must give serious consideration to Coca's theory,[2] "that the symptoms of serum disease are due to a specific altered reactivity of the protoplasm of some of the body cells, which is not mediated by antibodies." The main support for this hypothesis is found in the close resemblance of serum disease to the syndrome frequently produced by nonantigenic drugs from the point of view of incubation period, symptomatology, and the shortening of the incubation period upon reinjection. Regardless of the specific nature of these drug sensitivities, the mediation of antibodies in their mechanism has not yet been generally established. The fact that horse serum is antigenic does not necessarily exclude the possibility that it may, under certain circumstances, behave in a manner similar to nonantigenic excitants in the production of specific protoplasmic changes in certain cells of the body.

b. "Serum-Sickness" in Animals.—Serum reactions in lower animals have been described, which more or less closely resemble the serum disease of humans. The most outstanding examples of these reactions are found in the horse (produced by the sera of cattle, man, and rabbit), in cattle (produced by the serum of horse), and in the rabbit (produced by the serum of horse). Kopeloff[17] recently described symptoms in the monkey, *Macacus rhesus*, which, in some respects, simulated the symptoms of serum-sickness in human beings.

Fleisher and Jones[18] have continued their studies on "serum-sickness" in rabbits and have described symptoms in 53 per cent of their treated rabbits, which are very similar to those of human serum-sickness. The symptoms consisted of erythema and edema of the ears, heightened body temperature, and changes in the leucocytic blood picture. The syndrome occurred after an incubation period of not less than three

days, usually on the fifth or sixth day following a primary intravenous injection of horse serum. Five cubic centimeters of horse serum per kilogram of animal weight was the minimum amount required for the production of serum-sickness. A subsequent injection of serum in these animals could produce an "accelerated serum disease" (in three days or less), an "immediate" reaction (within eight hours), or "serum-sickness" with a normal incubation period. The time interval between the first and second injections was found to be an important factor in influencing the nature of the subsequent response. Immediate reactions became more numerous as the time interval between the first and second injections increased. After an interval of from three to four and one-half months, only immediate reactions developed.

The sera of normal horses varied widely in their ability to produce "serum-sickness" in rabbits. Their effectiveness in this respect ranged from 24 per cent to 93 per cent. Beef serum was less active than horse serum in producing "serum-sickness," while sheep and hog sera were found to be the least effective. Fleisher and Jones could demonstrate no constant relationship between the titers of antigen and antibody found in the blood of the rabbit and the appearance of "serum-sickness." A lack of correlation between the "serum-sickness" reaction in the rabbit and precipitin production was also reported by Khorazo.[19]

Further studies by Jones and Fleisher[18f, 18g] on the relationship of serum fractions to "serum-sickness" in rabbits revealed that pseudoglobulin was the fraction primarily responsible for the production of the condition. The euglobulin fraction was effective only when injected in large amounts. No symptoms were produced with the albumin fraction. No difference was observed between normal and immune sera in their ability to cause "serum-sickness" in rabbits.[18d]

The removal of lipids from horse serum diminished its power to produce "serum-sickness" in rabbits in many instances. Jones and Fleisher,[18h] however, observed no direct relationship between the amount of lipids removed from the serum and the diminution in its ability to produce "serum-sickness."

More recently, Fleisher and Jones[18i] have succeeded in removing from the serum the factor causing "serum-sickness" in rabbits by treating the serum with alkali and heat. This technique was not found applicable for the prevention of serum disease in humans.

An increase in the heterophile antibody titer in the serum of rabbits with "serum-sickness" was recently reported by Kemp and Baker.[20]

We thus find that "serum-sickness" of rabbits clinically resembles the serum-sickness of humans in many respects. The parallelism is continued in that changes in the precipitin and heterophile antibody titers have frequently been found to be associated with serum-sickness

in both species. In neither species, however, has a definite etiological relationship between the circulating antibodies and the symptoms of serum-sickness been established.

2. *Clinical Aspects.*—The incidence of serum-sickness varies in the reports of different workers. The *quantity* of serum administered appears to be a factor in the frequency of serum-sickness.[21-24] This may, to a certain extent, explain the high incidence of serum-sickness which some workers have reported following the use of antimeningococcic serum[11] and Type II antipneumococcic serum.[4a] Most workers have reported higher incidence and greater severity of serum reactions following the use of antistreptococcic and antipneumococcic sera than occur after the administration of diphtheria or tetanal antitoxin.[23]

The *animal source of the serum* also influences the incidence of serum-sickness. Hog serum is said to produce serum-sickness as often as horse serum.[27] Avian serum (Kyes' antipneumococcic serum derived from the barnyard fowl) is reported to be devoid of factors which produce serum disease.[105]

Serum-sickness following the use of unconcentrated rabbit antipneumococcic serum occurs in about 40 per cent of administrations.[26, 28, 29a, 30] This incidence is higher than that produced with concentrated horse serum[30] but lower than that obtained with unconcentrated horse serum.[28] An analysis of the available statistics[25, 29b, 31, 32] in serum administration in 368 cases reveals that, with concentrated rabbit serum, there is a definite reduction in the incidence of serum-sickness to about 26 per cent of administrations.

The *route of administration* of serum is undoubtedly a factor in the incidence of serum-sickness. The intravenous injection of serum seems to have increased its frequency. An interesting report by Wilke[106] states that the oral administration of bovine serum in children for the purpose of nonspecific foreign protein therapy was not followed by serum-sickness. Horse serum administered by this route, however, was frequently followed by typical serum disease.[108]

Age[21, 22, 33, 34] and *sex*[13, 21] have no bearing on the incidence of serum-sickness. The American Indian[35] and the negro[21, 36] seem to be less susceptible to serum disease than members of the white race.

In the majority of patients the symptoms of serum-sickness follow the primary injection of immune horse serum after an *incubation period* of from six to fourteen days, the onset occurring most frequently on the eighth or ninth day.[22] In Hunt's series[21] of almost 4,000 cases, serum disease appeared before the eleventh day in 85.8 per cent of the affected cases. The longest incubation periods reported were twenty-eight[21] and thirty days.[37] The development of serum-sickness following reinjection of serum may be considerably accelerated. This aspect of the subject will be discussed later.

Reporting on the *duration of serum-sickness,* Bullowa[13] stated that it lasted from one to three days in 53.5 per cent of his patients, from four to seven days in 35 per cent, and a longer period in 10.9 per cent.

The characteristic *symptoms* of serum disease, which include fever, arthralgia, lymphadenopathy, and cutaneous eruptions, are too well known to be discussed here. Among the unusual symptoms recently reported are gastrointestinal hemorrhage, hematuria, edema of the larynx, severe local purpura,[23] and icterus and hepatic atrophy.[38] The occurrence of acute abdominal crises simulating surgical conditions of the abdomen has been reported.[13, 39, 40]

The characteristics of urticaria in serum-sickness have been reviewed by Hopkins and Kesten[42] and by Waldbott.[41] Waldbott reported an absence of blood eosinophilia in sixteen consecutive cases of serum-sickness. Anghelesco[43] reported no constant change in the sedimentation rate in serum-sickness.

Additional instances of *recurrent attacks of serum-sickness* following the primary serum injections have been reported.[21, 22] These have been explained by Coca[1, 2, 44] and Hooker[45] as separate reactions to the specifically different protein constituents of the serum. As many as four distinct attacks of serum-sickness have followed a single injection of whole horse serum.[23]

Clark[46] has recently reported several cases of serum-sickness in which distinctive structural changes in the heart and large vessels were found. They consist primarily of proliferation of histiocytes in the endocardium and in the intima of the large vessels, accompanied by stimulation of the interstitial mesenchymal tissue of the myocardium. These findings, while not constantly present in serum disease, were absent in twenty-three patients treated with serum, in whom serum-sickness failed to develop. The question needs further study.

Much has recently been written on the *neurologic complications* of serum disease. The most common symptom has been neuritis, commonly involving branches of the cervical and brachial plexus[47-49] and occasionally resulting in flaccid paralysis. Optic neuritis,[50a, 51] iritis,[52] inner ear deafness,[53, 54] Ménière's syndrome,[55] and laryngeal nerve paralysis[56] have also been recorded. Central nervous system involvement[57-59, 60b, 61] and psychosis[60a, 62, 63] may also occur.

These symptoms are commonly explained on the basis of a perineural edema occurring during serum-sickness and resulting in an ischemic paralysis of the nerve trunks or peripheral nerves.[50, 57, 63, 64] These complications are rare in children.[65] They may be produced by refined sera[66] but are said not to occur after the administration of normal horse serum.[62] They may be the only manifestation of serum-sickness.[67] They tend to recur in the same patient upon reinjection of serum.[63b, 68-70]

Neurologic complications may persist from six months[71] to two years.[72] They usually disappear completely, but Bennett[64] reports that 21 per cent of those affected may be left with a residual weakness.

As yet, few serious complications have been reported following the use of rabbit immune serum.

Various methods have been suggested for the *prevention* or modification of serum-sickness. They include the daily intravenous administration of ascorbic acid,[73, 74] the use of an antiketogenic diet,[75] the oral and intramuscular administration of histaminase,[16] and the use of autohemotherapy given shortly before[76] or after the serum injection.[77] Voss[10a, 10b] recently recommended that convalescent serum from patients recovering from serum-sickness be given intravenously within seventy-two hours after the injection of animal serum. An evaluation of the actual prophylactic value of these recommended procedures must await their application in large series of cases.

The future of prophylaxis in serum disease seems to lie in the direction of *purification and concentration of antitoxic sera.* Fractional salt precipitation, the most commonly employed method of purification and concentration, has been only moderately effective in reducing the incidence of serum allergy. The more recently described method of selective peptic digestion, which has been perfected by Parfentjev[78] in this country, seems to hold out more promise. By a carefully controlled process, using pepsin in a limited pH range, digestion of between 70 per cent and 80 per cent of plasma proteins can be effected. The antibodies may then be removed by dialysis and "salting-out" of the pseudoglobulin fraction. The antitoxin concentration of the solution is not impaired by the process. However, by comparative skin tests on human beings and by animal experiments, Weil, Parfentjev, and Bowman[79] have demonstrated that there is a marked loss of antigenic property in this modified globulin antitoxin.

Pope[80] in England and Grabar[81] and Hansen[82] in France, employing similar principles, have also demonstrated the value of this method of purification in the preparation of therapeutic sera.

Clinical confirmation of the effectiveness of these procedures in diminishing the incidence of serum-sickness and serum reactions has already been brought out by several workers. Bradshaw[83] administered to 793 children prophylactic doses of scarlet fever antitoxin (0.75 c.c. containing 75,000 original neutralizing units) prepared by Parfentjev's method. In this series, only 10 cases of mild serum-sickness resulted, an incidence of only 1.3 per cent. Hutchinson[84] reported recently on the results of treatment in 200 cases of diphtheria with antitoxin prepared by Pope's technique. No cases of serum disease occurred in the entire series, even though 50 of the patients had had a previous administration of serum. In 100 patients, who received antitoxin intravenously, no immediate reactions of consequence resulted.

Once serum-sickness has developed *treatment* becomes purely symptomatic. Measures which have been favorably recommended include

the administration of calcium,[13, 85, 86] salicylates, epinephrine, ephedrine, and ergotamine tartrate.[82] Autohemotherapy[76, 77] and histaminase[16] have also been recommended for their favorable influence in allaying the severity of symptoms.

Although the symptoms of serum-sickness may be severe, fatalities from the disease itself have not been reported. Complete recovery is the usual result with the occasional exception of neurologic complications, which may not completely clear.

The possibility of the development of serum disease or any of its complications should not be considered a contraindication to the use of serum therapy whenever it is indicated.

B. ACCELERATED SERUM-SICKNESS

One of the greatest variables in the clinical course of serum disease is the length of the incubation period. As previously pointed out, the free interval between the primary injection of the serum and the appearance of symptoms usually varies from six to fourteen days, with the onset most frequently occurring on the eighth or ninth day. Following a second injection of serum, von Pirquet and Schick[89] reported accelerated serum reactions from the second to the sixth day. Such reactions, according to Tuft, may occur even on the first day.[36] In Davis' series,[90] the average day of onset of serum-sickness after reinjection of serum was the sixth day. Davis points out that, in eighteen cases with a history of previous serum administration, the incubation period was from seven to ten days, thus indicating that serum-sickness is not necessarily accelerated in its onset following a second administration of serum, a point which Coca[1] had also emphasized. In twenty-two of Davis' patients with no history of previous serum administration, the incubation period was only from one to three days. This bears out the experience of others[36] that it is possible to obtain an accelerated serum-sickness without previous serum administration. The significance of this fact in the theoretical conception of an antibody mechanism in serum-sickness is obvious.

Reinjection of serum during the normal incubation period following a primary injection does not hasten the onset of serum-sickness.[44] Once this period has elapsed, any subsequent injection of serum may be followed by an accelerated serum-sickness.[36] The latter is most frequently seen following reinjections given from three to five months after the primary injection. The development of an accelerated type of serum-sickness becomes less likely as this interval increases.[91] A cutaneous test with serum is of no value in foretelling the occurrence of accelerated serum-sickness.

C. LOCAL SERUM-SICKNESS

The occurrence of a local reaction at the site of the serum injection after an incubation period, similar to that of typical serum-sickness,

may be the only manifestation following the subcutaneous or intramuscular administration of antitoxin.[21, 90] According to Seegal and Khorazo,[92] such reactions have usually appeared within seven days after injection. These workers studied the ability of the immune sera of the horse, sheep, rabbit, and cow to induce local serum-sickness. The intracutaneous injection into humans of 0.1 c.c. of undiluted sheep or horse immune serum was most effective in producing local serum disease. Bovine serum, purified horse globulin, and bovine globulin were less effective. Rabbit serum was reported to be almost inactive in this respect. Local serum-sickness following the intracutaneous injection of rabbit serum has, however, been reported by Mote and Jones.[93a] Rackemann and Simon[94] have also reported local serum-sickness following the intracutaneous injection of guinea pig serum.

Sporadic reports[95] of the development of necrotic lesions from local serum-sickness reactions continue to appear in the literature. Kohn,[95g] in an analysis of these reports, pointed out that such necrotic reactions have almost invariably occurred in patients who had received immune serum at some previous time. In most instances, this interval has been from seven weeks[95d] to three years.[95e] The reaction which he described in his own case report is more or less typical. A blanching and soreness of the buttock developed at the site of injection. This gradually became purpuric and then necrotic. The reaction reached its height from forty-eight hours[95e] to five days[95g] following the injection. In two of the reported cases[95e, 95h] the necrotic reaction appeared coincident with generalized serum-sickness. In those instances in which repeated doses of serum were given at relatively short intervals, the necrotic reaction involved only the last site of injection. In Kohn's case, it appeared forty-eight hours after the last of three intramuscular injections, given on the first, third, and fifth days. In another case reported by Irish and Reynolds[95f] the reaction developed shortly after the last of five injections given on the first, second, third, seventh, and eleventh days. In Gougerot's[95e] patient, it developed following the first reinjection of serum. The necrotic reaction may occur even when there is no evidence of cutaneous sensitivity to horse serum.[95h] Incision of the necrotic areas usually revealed no sign of bacterial invasion.[95k] It may subside without incision.[95a, 95e, 95h] Death may occasionally result from this complication,[95i] but such an outcome is rare.

Some observers have loosely applied the term Arthus phenomenon to these reactions because of their apparent resemblance to the necrosis which may develop in sensitive rabbits following repeated subcutaneous injections of the antigen. The choice of this term is unfortunate. Recent investigations[109] point more and more to the correlation between the high titer of precipitin and the development in the rabbit of the Arthus phenomenon. The participation of precipitin or of any other antibody in these necrotic lesions in human beings has never

been demonstrated. The reference to this necrotic lesion as a Schwartzman reaction should also be discouraged in the absence of any definite information as to the mechanism involved. The possibility of severe local reactions following the intramuscular injection of human serum must also be kept in mind. In view of the fact that all of these reactions occur so rarely and information concerning them is so meager, it would be advisable, for the present, to postpone any attempt at an immunologic explanation for them.

II. SERUM REACTIONS

It has already been pointed out that serum disease, under ordinary circumstances, presents a more or less characteristic syndrome, which develops typically after an incubation period of several days. In contradistinction to this particular form of allergy there are various types of serum reactions, which develop while the serum is being administered or within a few minutes thereafter. These are commonly known as immediate reactions. There are several types of immediate reactions, of which only part appear to be based on immunologic mechanisms. Their symptomatology is varied. Frequently the reactions do not appear until several hours later or until the following day, in which case they are commonly referred to as delayed reactions. Since serum disease following the reinjection of serum may be so accelerated that it appears on the second and even on the first day after the administration of serum, considerable difficulty has arisen in differentiating between the latter and the delayed types of reactions. Thus, an urticaria occurring on the second day after injection has been designated by some as a "delayed serum reaction" and by others as an "accelerated serum-sickness." Since accelerated serum disease starting within forty-eight hours after injection is relatively infrequent, it seems convenient, for the present, to call reactions occurring within that period either "immediate" or "delayed" depending upon how soon they follow after the injection. However, this does not necessarily preclude a diagnosis of accelerated serum-sickness within the first two days if the symptoms are sufficiently characteristic (not merely an urticaria) to warrant it.

A distinction between immediate and delayed reactions may rest upon differences in mechanisms and upon quantitative factors. It is obvious that the intravenous introduction of serum may induce an immediate reaction which might have been considerably delayed in its onset, had the serum been given subcutaneously and its absorption thereby retarded.

In the absence of a knowledge of the mechanisms involved, a classification of immediate and delayed reactions, therefore, becomes most difficult. Only the nature of the atopic form is understood, and even here our knowledge is incomplete. The classification employed below is obviously inadequate. It is used merely to facilitate the presenta-

tion of the material. Other tentative classifications have recently been suggested by Tuft,[36] Bullowa,[13] Reimann,[37] Lord and Heffron,[96] Rudolph and Cohen,[91] Heffron,[107] and others.

1. *Nonspecific Immediate or Delayed Reactions: a. Collapse.*—This reaction, consisting of a flushing of the face, dyspnea, cyanosis, lumbar or abdominal pain, rapid, weak pulse, and apprehensiveness, is usually transient and relatively infrequent. It occurred in only 7 per cent of the series of 1,755 cases reported by Lord and Heffron.[96] Bullowa[13] considers these reactions to be due to a vascular reflex as a result of the slight trauma of the intravenous injection. He recommends artificial respiration, hot blankets, and routine shock treatment for their control.

b. Thermal or Febrile Reactions.—The thermal or febrile reactions are characterized by chill, elevated temperature, delirium, rigor, and malaise. They usually appear from forty-five to ninety minutes after the intravenous injection of serum, but may occur earlier and even during the injection.[25c] Lord and Heffron[96] reported an incidence of 17.8 per cent of thermal reactions with three fatalities in their series. Thermal reactions have occurred rather frequently with the intravenous use of antipneumococcal rabbit serum. Although usually not severe, such reactions have been known to cause extreme hyperpyrexia and to result in fatalities.[26]

Some of the chill-producing factors in immune sera are still unidentified. Some of them are still present in concentrated and refined sera.[107] Goodner, Horsfall, and Dubos[97] have reported that heating rabbit immune serum to 58° C. for thirty minutes and then adsorbing it with sterile washed kaolin for fifteen hours at 4° C. will remove most of the chill-producing substances.

For the control of thermal reaction, Bullowa[13] recommends the administration of amyl nitrite perles and warns against further serum administration until the temperature has subsided. Other lots of sera may then be tried, but if the febrile reactions are very alarming, further attempts at serum therapy may have to be discontinued.[96]

It has been pointed out that the chill-producing effects of certain antipneumococcal sera may be considerably diminished by administering them by the intramuscular route.[98]

To prevent thermal reactions following antipneumococcal rabbit serum administration, MacLeod[99] recommends the oral administration of acetylsalicylic acid just prior to the serum injection. He has not been impressed with the effectiveness of calcium chloride, the intravenous use of which has been recommended[100] for the relief of the chill reaction. However, no completely satisfactory means have yet been found either to prevent or to relieve the chill reaction which follows the use of serum containing a high concentration of the chill-producing substance.

2. *Specific Immediate and Delayed Reactions: a. The Atopic Serum Reaction ("Allergic Shock").*—This usually takes the form of an immediate shocklike type of reaction which occurs typically during or within a few minutes after the injection of serum in individuals with an atopic ("natural") hypersensitivity to the serum. Strong positive cutaneous and ophthalmic reactions to tests with serum are frequently observed in this group of patients.[44] They often manifest a concomitant sensitiveness to horse dander which may manifest itself as bronchial asthma or allergic rhinitis when they are in the vicinity of horses.

In such patients, the initial or primary injection of horse serum, even in very small amounts, is likely to be followed by an immediate, severe, and even fatal reaction. The classic example of this type of reaction is the case reported by Boughton in 1919 in which death resulted from the administration of *one minim* of horse serum given intravenously to the patient, a "horse asthmatic." Among recent reports is Friedman's[101] case history of a 6-year-old child with a history of bronchial asthma and infantile eczema who died within eight minutes following an intracutaneous test with 0.05 c.c. of horse serum. Death was preceded by generalized urticaria, abdominal pain, and cyanosis. Lobo[102] described the death of a 1-year-old child with an "exudative diathesis" which resulted from the subcutaneous injection of 5 c.c. of antidysentery serum. Vaughan and Piper,[103] in reviewing the literature from 1923 to 1935, found thirty-five instances of death following the administration of horse serum, six of which followed intracutaneous tests with undiluted horse serum. Tuft[36] estimated that fatal reactions of this type occur approximately only once in every 70,000 individuals injected.

The reactions in these cases may start even before the needle has been withdrawn. Severe pruritus at the site of injection or generally distributed, and varying degrees of urticaria, angioneurotic edema, sneezing, rhinorrhea, and bronchial asthma, may appear simultaneously or follow each other in rapid succession. Death may ensue within a few minutes.

Because of the rapidity of its development and its severity, this type of reaction is extremely difficult to control. Once the reaction is recognized large doses of epinephrine should be administered hypodermically, and, if necessary, intravenously. Bullowa[13] found that atropine, caffeine, and camphor were virtually useless in combating this type of reaction. This has also been the experience of many allergists.

The nature of the immediate atopic serum reaction is probably the same as that encountered in the immediate constitutional reactions following the administration of pollens and similar antigenic substances in the prophylactic treatment of hay fever and asthma. Usually present in these cases are the two factors participating in the typical atopic

reaction, namely, the atopic reagin and the atopic shock tissue.[44] The union of the injected horse serum and the reagins, which are fixed in the shock tissues, results in the excitation of the latter. Since the reagins sensitize the skin and mucous membranes, their presence is usually marked by positive cutaneous and ophthalmic reactions.

A point which is frequently overlooked is the fact that the atopic shock tissue may be nonspecifically excited, even in the absence of demonstrable reagins and of a positive cutaneous reaction. This possibility is well illustrated in a case which was brought to our attention.

E. D., 19 years of age, suffered occasional attacks of asthma but had been free of symptoms for a year. He had received no previous injections of antitoxin or horse serum. Following an injury, he was given a prophylactic injection of tetanal antitoxin. After several days he experienced some malaise, which was diagnosed as serum-sickness despite the absence of any frank symptoms. On the eighteenth day after the injury, symptoms developed suggestive of tetanus. On admission to the hospital on the twenty-first day, a cutaneous test with horse serum was said to have been negative. He was given 10,000 units of tetanal antitoxin intramuscularly with no untoward symptoms. Two and one-half hours later a similar dose was given intraspinally. No symptoms of serum allergy were noted. After another interval of two and one-half hours, an intravenous injection of 10,000 units was started. Within two minutes, a severe asthmatic type of dyspnea developed, and cyanosis became marked. A generalized "goose flesh" appeared, and a thin fluid secretion was seen to pour from the nose. Despite large intravenous doses of adrenalin, death followed within a few minutes. Autopsy revealed edema of larynx, glottis, and bronchial mucous membranes and marked distention of the lungs.

It seems probable that the atopic shock tissue in this case was nonspecifically stimulated by the intravenous dose of a foreign protein. The intramuscular and intraspinal doses, given several hours before the intravenous injection, failed to reveal any evidence of a specific sensitivity. This case also illustrates the unreliability of so-called "desensitizing" procedures when serum is to be given intravenously.

In the patient atopically sensitive to horse serum it is quite usual to find some degree of associated sensitivity to horse dander. These sensitivities may exist without any history of a previous injection of horse serum. The theoretical considerations involved in explaining this phenomenon have been completely reviewed by Tuft.[110] Clinical and experimental studies have shown that horse dander contains a small amount of horse serum antigen. Hence, sensitization of atopic individuals by the inhalation of horse dander might sensitize to horse serum as well. Conversely, the injection of horse serum into atopic individuals might also result in a horse dander hypersensitiveness.

A possible type of immediate serum reaction mediated by the atopic reagin, which may occur in the nonatopic as well as in the atopic person, should be kept in mind. This atopic-like reaction undoubtedly occurs, although it has not yet been recognized as a particular type of reaction by the clinician. Tuft[104] has pointed out that atopic reagins

frequently appear in the circulation during the course of serum disease and persist for several weeks thereafter. Since the mucous membranes[111] and skin of nonatopic individuals possess the power to fix reagin, it is probable that such antibodies will temporarily sensitize the individual to serum. A positive cutaneous, and even a positive ophthalmic test, may be expected in the nonatopic individual while the reagins are present in his blood and tissues. In the absence of the atopic shock tissue, however, the immediate reaction, following the administration of horse serum, should be milder than that occurring in the atopic person.

b. Nonatopic Serum Reactions.—According to Tuft,[36] previous administration of serum is one of the most important factors in determining the incidence of these types of reactions. This statement finds support in the report of Davis,[90] who recently reviewed the histories of 4,835 patients who had received concentrated diphtheria antitoxin. Among 175 of these, who had received serum previously, 7.3 per cent developed immediate reactions and 69 per cent accelerated reactions.

The type of serum reaction which occurs following the reinjection of serum is to some degree dependent upon the nature of the serum previously injected, the route of its administration, and the quantities given. Gordon and Creswell (1929) found that reinjection of therapeutic sera produced serum reactions in 43 per cent of those who had previously received immune serum, in 74.1 per cent of those who had previously received diphtherial toxin-antitoxin, and in only 18 per cent of those who had not received any serum.

It is now common knowledge that large amounts of serum are not essential for sensitization. Although diphtherial toxin-antitoxin contains only about 0.0001 c.c. of horse serum per dose, immunization with two or three injections of this material was able to sensitize to horse serum in 25 per cent of cases in Hooker's[112] series and in 27.9 per cent of Tuft's cases.[113]

The stages in the development of some of these nonhereditary types of hypersensitiveness, their experimental production with rabbit serum,[114, 93b] guinea pig serum,[94] as well as with horse serum,[113, 115] and the antibody studies in these conditions have been presented in detail in one of our former reviews[116] and will not be repeated at this time.

One of the immediate types of reaction of the nonatopic type has been described in detail by Rudolph and Cohen.[91] At the time of injection or shortly thereafter the reaction develops. The person becomes apprehensive and sweats profusely. The face becomes flushed, the eyes congested, the lids edematous, and a generalized urticaria usually develops. Nausea, vomiting, and general prostration frequently occur. However, Tuft[36] has pointed out that, despite the presence of dyspnea in these reactions, no asthmatic breathing is heard.

Of interest is the scarcity of reports of the association of joint symptoms with the "immediate" serum reactions. Tuft[113] mentioned one case which did not come under his direct observation but which was reported to him. Brown and Finland[25a] observed two cases in which fleeting joint symptoms at the time of injection were the only manifestation of the "immediate reaction." This is in contrast to the accelerated form of serum-sickness, in which joint pains of a prolonged and severe nature are quite common.

Positive cutaneous reactions to horse serum commonly occur in the nonatopic forms of serum allergy. They are not dependent upon the presence of the atopic reagin. Positive ophthalmic reactions to horse serum are unusual in these types of sensitivity.

Whether or not the immediate reaction which occurs on reinjection of serum is "anaphylactic" in nature is still a moot question. According to Tuft,[36] the "immediate" serum reaction "is only possible in a sensitized individual." Many observers[13, 36, 91, 103] still favor the concept that this type of serum reaction is an example of an anaphylactic reaction in man.

Coca[1, 2, 44] has repeatedly pointed out the weaknesses in this hypothesis. The immunologic mechanism involved in many of these reactions is still unknown. In the absence of any new evidence on the subject, the reviewers are reluctant to subscribe to the anaphylactic hypothesis to explain these reactions.

A. THE ADMINISTRATION OF SERUM

One cannot prognosticate with certainty the occurrence of an untoward reaction following the injection of a therapeutic serum. There are, however, certain circumstances which are more unfavorable than others for serum administration and certain danger signals which are ominous.

Fatalities or severe immediate reactions following serum administration are more likely to occur in the atopic than in the nonatopic group. A positive personal or family history of asthma, hay fever, vasomotor rhinitis, infantile eczema, or food or drug sensitivity should be sufficient to mark the patient as an atopic or as a potentially atopic patient. A history of "horse-asthma" multiplies the danger of administration to an almost prohibitive extent. Bullowa[13] does not consider a history of asthma an absolute contraindication to the administration of therapeutic pneumococcic serum if the ophthalmic reaction to horse serum is negative. He has given antipneumococcic serum without ill effects to fifteen asthmatic patients who were not horse-serum-sensitive. Virtually the same opinion is held by Lord and Heffron[96] who have given pneumococcic serum to fifteen patients with a history of bronchial asthma and to two patients with hay fever, without unfavorable reactions. These workers feel, however, that

more than average precautions should be exercised in the administration of serum to atopic patients. This also represents Cecil's[117] attitude on this question.

The opinions of the above workers are primarily based upon their vast experience in serum therapy in pneumonia. In connection with this illness it is important to keep in mind that such patients, as a rule, are acutely ill and have high temperatures. Such circumstances are most favorable for the inactivation of the atopic shock tissues, thereby rendering the subjects anergic.[118, 88a] A striking example of this was encountered by one of the reviewers in the case of an asthmatic, aged 3 years, who was extremely sensitive to egg. (Case history and serum studies have been described previously.[142]) Despite the grave symptoms which usually resulted from the minutest contact with egg in food, this child, following a pneumonia, was inadvertently given an entire soft-boiled egg without experiencing the slightest symptoms of allergy. Several weeks after discharge from the hospital, clinical sensitivity to egg returned with all its previous severity, producing asthma, rhinitis, angioneurotic edema, urticaria, vomiting, and collapse.

The experiences of Bullowa, Lord and Heffron, and Cecil with pneumonia should, therefore, be interpreted in the light of the illness which they are treating. It cannot be assumed that the exemption from untoward accidents which they enjoyed would occur in the administration of horse serum to atopic individuals who are not acutely ill. Moreover, even in patients with pneumonia, it is possible that an absolute state of anergy may not be established, in every case, in the very early stages of the disease or even at the height of the illness. The reviewers are of the opinion that, in atopic individuals, the milder the illness, the greater the risk of intravenous therapy.

Another point to which workers attach variable degrees of importance in attempting to foretell the incidence of severe reactions is the history of a previous administration of serum. This point has already been discussed under "accelerated serum-sickness" and "immediate reactions." Previous contact with serum is not in itself a contraindication to the use of serum. In atopic persons, however, previous contact heightens, to some extent, the hazard already existent, for, as Tuft has pointed out, induced sensitivity occurs more frequently in atopics than in nonatopics[113] and is likely to be more lasting.[110] The presence of atopic reagins during or after serum disease is also a stronger contraindication to serum therapy in an atopic than in a nonatopic person.

Valuable information as to the presence of serum allergy may be obtained by cutaneous tests. Unfortunately, all positive reactions are not of the same clinical significance. Yet the presence of a positive reaction may be of some value as a warning of potential danger, par-

ticularly in the atopic patient. Cutaneous testing is, therefore, a decidedly worth-while procedure and should be employed before the therapeutic administration of any serum.

Lord and Heffron[96] are of the opinion that "horse-asthmatics" should not even be tested for serum hypersensitiveness and that such cases should be excluded from serum therapy. Warner[119] and Wood[31] are of the same opinion in respect to the use of rabbit serum in rabbit-sensitive asthmatics. While serum hypersensitiveness usually accompanies horse dander sensitivity, such an association cannot be considered inevitable. Tuft[110] has cited the case history of an asthmatic child with respiratory symptoms following exposure to horse dander, who, nevertheless, showed a negative reaction to horse serum and tolerated the administration of immune serum without any allergic symptoms whatsoever. Cutaneous testing with horse serum is, therefore, indicated, despite the history of allergy to horse dander, although extraordinary precautions should be adopted in testing such patients.

For cutaneous testing, Rudolph and Cohen[91] have recommended the scratch technique, to be followed in the case of negative results by the intracutaneous method. Their obvious purpose is to prevent the occurrence of constitutional reactions as a result of testing. Most workers, however, prefer the intracutaneous test, taking the necessary precautions to prevent constitutional reactions.[36, 44, 85, 88b] In the nonatopic patient, a 1:10 dilution of horse serum may be used. In the atopic patient, it is advisable to start with a 1:100 dilution.[36, 44] In the presence of a history of horse sensitivity, testing should begin with a 1:1,000 or greater dilution. If negative reactions are obtained with high dilutions, subsequent tests should be made with dilutions of 1:100, 1:10, and undiluted horse serum. In a recent report of death in an atopic child from intracutaneous testing with horse serum, 0.05 c.c. of undiluted horse serum had been used.

Regardless of dilution, no more than 0.01 or 0.02 c.c. of extract should be injected intracutaneously for testing purposes.[36, 85] The common practice of injecting intracutaneously 0.1 c.c. of horse serum[13, 90, 120-123] or of rabbit serum[26, 28, 31] is to be decried. The use of such a large amount of testing material results in many false positive reactions in nonsensitive patients and increases the possibility of constitutional reactions in atopic cases.[88b] Coca and Plummer[125] recommend for testing with normal rabbit serum the technique already described for horse serum.

Frequently, when normal horse serum is not available for testing purposes, the therapeutic immune serum is employed. The recent demonstration by Foshay[124] that immune serum may produce an immediate reaction consisting of erythema and edema (E-E reaction) should discourage this practice, for the reaction thus obtained may be

confused with the specific sensitivity reaction to horse serum. The E-E reaction, however, lacks a wheal and can therefore be differentiated by this characteristic.

A negative cutaneous reaction to undiluted horse serum indicates a minimum of risk for the injection of horse serum in all types of patients by all routes of injection. On the other hand, the reviewers have already presented the case history of a death following the intravenous injection of serum in an asthmatic with a negative cutaneous reaction to horse serum. Under the circumstances, intravenous serum administration must be performed with more than the usual precautions in the atopic person, even in the presence of a negative cutaneous reaction. The negative cutaneous reaction does not, of course, exclude the possibility of nonspecific reactions (e.g., thermal, collapse) following intravenous administration of serum.

Most workers agree that some positive cutaneous reactions are clinically unimportant and are no contraindication to the use of animal serum. There is need, therefore, for additional means of differentiating between those types of positive reactions which are clinically significant and those which are not. The ophthalmic test is of great assistance in furnishing information on this point. For this purpose, Tuft[36] has recommended putting a drop of undiluted horse serum in the eye of patients with negative or slightly positive cutaneous reactions. Dilutions of 1:10 or 1:100 should be employed when stronger cutaneous sensitivity exists. Ophthalmic reactions are often severe and in atopic individuals may cause constitutional reactions.[126]

Ophthalmic reactions are frequently negative in cases with positive cutaneous reactions. This is frequently the case in cutaneous sensitivities which have been acquired as a result of previous serum administration. When the ophthalmic reaction is negative, the danger of a serious serum accident is considerably diminished.

Positive ophthalmic reactions rarely, if ever, occur when the cutaneous reaction is negative.[36] A positive ophthalmic reaction is indicative of mucous membrane sensitivity. On the whole, it is a better index of constitutional sensitivity than the cutaneous test. It is a danger signal which should be respected. It occurs more frequently in the atopic type of sensitivity than in any other and is usually mediated by the atopic reagin. It represents the most dangerous circumstances under which serum may be injected. Hence, there is complete justification for the position taken by many workers[37, 44, 85, 96, 119, 125-127] that a positive ophthalmic reaction is a contraindication to the administration of serum.

Positive ophthalmic reactions may occur in the absence of reagins. In a case quoted by Coca[2] positive cutaneous and ophthalmic reactions were observed in an atopic individual, but no atopic reagins could be detected in the circulation. Despite the absence of these antibodies, the patient

suffered a severe constitutional reacton followng the intramuscular administration of 1 c.c. of therapeutic horse serum. This affirms the danger of serum administration in the presence of a positive ophthalmic reaction even in the absence of reagins.

The presence of atopic reagins in the patient's blood may be detected by the Prausnitz-Küstner technique (indirect method of testing[88b]). By ruling out the presence of these antibodies with this method of testing, it has been possible to administer serum to asthmatic patients with positive cutaneous reactions to horse serum, under circumstances which would have ordinarily been considered as prohibitive.[128, 129]

During the last two years an intravenous test has been recommended and commonly employed in connection with the administration of immune rabbit serum.[28] The need for such a test was based upon the assumption that the usual intracutaneous technique, when applied to rabbit serum, produced too many nonspecific reactions and was therefore unreliable. In the earliest practice, 0.1 c.c. of a 1:10 dilution of normal rabbit serum in 5 c.c. of saline was slowly administered into the vein.[28] A fall in the arterial systolic pressure of at least 15 mm. of Hg and an increase in the cardiac rate of at least 15 beats per minute, both occurring within at least five minutes after the administration of the test dose, were considered indicative of a positive reaction. Because of the occurrence of several severe reactions in allergic individuals, this technique has more recently been modified so that, in cases of this type, 0.01 c.c. of a 1:10 dilution in 5 c.c. of saline is slowly injected intravenously.[29, 96] MacLeod[39] and Warner[119] have cautioned against the application of this test until the cutaneous and ophthalmic tests have been tried and proved to be negative.

The assertion that rabbit serum gives a greater number of nonspecific cutaneous reactions than horse serum has not been borne out when intracutaneous tests were made with 0.01 c.c. of a 1:100 or of a 1:10 dilution of normal rabbit serum. Employing this technique, Brown,[126] as well as the reviewers, found no excessive irritative properties in normal rabbit serum even when the tests were performed on the skins of atopic patients.

The once prevalent opinion that all patients who are sensitive to serum could be "desensitized" by gradually increasing subcutaneous injections of horse serum is now being generally challenged.[36, 44, 85] Enough fatalities[36] have occurred, despite "desensitization," to discredit this procedure as a guarantee against serious accidents. While such methods may reduce somewhat the frequency and severity of reactions following reinjection of serum, they have proved least reliable when employed in atopic subjects.

Desensitization procedures, however, are not entirely valueless. Following the intracutaneous or subcutaneous injections of minute doses of

horse serum, the development of constitutional reactions may warn the clinician of the extreme intensity of the sensitivity which is present. He may then discontinue the administration, while symptoms can still be controlled by adrenalin. With large doses of serum or with the intravenous administration of small doses, adrenalin cannot be relied upon to prevent or control severe immediate reactions. Tuft[36] has described in detail the procedure to be employed in the administration of serum to patients in whom untoward reactions may be anticipated.

Anesthesia has also proved untrustworthy as a preventive of allergic serum reactions. Quill[130] reported the case of a man who died within three minutes following a prophylactic injection of tetanal antitoxin while under nitrous-oxide-ether narcosis. Koontz,[131] therefore, has discouraged the common practice of administering tetanal antitoxin to surgical patients under anesthesia without preliminary sensitivity tests.

B. THE INFLUENCE OF HYPERSENSITIVENESS TO SERUM ON THE UTILIZATION OF THERAPEUTIC SERA

Davidsohn and Hunt[132] reported that when horse serum or horse-immune serum was injected into a normal rabbit, the serum was eliminated gradually for seven or eight days until precipitins appeared in the circulation. Thereafter elimination proceeded at a more rapid pace. However, when horse serum was reinjected into a sensitized rabbit, it rapidly disappeared from the circulation. This was in accord with the early studies of Glenny and Hopkins.[133]

The finding of accelerated elimination of antigen in sensitized animals has been confirmed by the more recent experiments of Kahn and McDermott,[134] Culbertson,[135] Falchetti,[136] Bernabi,[137a] and Schmid.[138a] Likewise, Bieling and Oelrichs[139] demonstrated that, in rabbits sensitized to horse serum, horse serum antitoxin proved less effective against diphtherial toxin than in normal rabbits. On the other hand, the therapeutic value of bovine and sheep antitoxins was only slightly inhibited in horse-serum-sensitized rabbits.

Studying the effects of route of administration upon the height of antitoxin curves in rabbits sensitized to horse serum, Bernabi[137b] obtained interesting results. The highest titer of antitoxin in the blood was demonstrated following the intravenous injection of the antitoxin, although the amount and its duration in the blood stream were considerably less than in normal animals. Following intraperitoneal and subcutaneous administrations, low titers of brief duration were obtained. Following an intracutaneous injection, the presence of antitoxin in the blood stream could not be detected.

The earlier experimental studies in sensitized human beings (and also in animals) were critically reviewed by Hooker and Follensby[140] in 1931. In their own investigations, they studied the duration of local passive immunity produced by the intracutaneous injection of

scarlatinal antitoxin. Persons with a negative immediate cutaneous reaction to horse serum retained an effective amount of the antitoxin for more than twenty-four hours, while those with a positive reaction were locally protected for less than four hours. The authors, however, were aware of the limitations of these experiments in their application to the therapeutic administration of antitoxin in allergic patients.

In a more recent study, Davidsohn and Hunt[132] analyzed the therapeutic effects of horse serum antitoxin injected into 40 diphtheria patients who manifested serum reactions within forty-eight hours after the administration. The clinical results obtained in this group were compared with those in another series of 164 patients who had experienced the normal (late) type of serum disease, and with those in a third group of 97 patients who had manifested no serum symptoms of any type. In the two latter groups, the antitoxin proved equally effective. Therapeutic results appeared to be less satisfactory, however, in patients who experienced the early serum reactions. A greater number of complications also occurred in this group. The authors, therefore, advised that, whenever the administration of horse-immune-serum is followed by an immediate or markedly accelerated serum reaction, additional doses of antitoxic serum be given, preferably from an animal other than the horse. The anamnestic evidence upon which these conclusions are based is subject to obvious limitations. Acceptance of the results, therefore, awaits confirmatory studies.

Madsen[141] and his co-workers found a true relationship in the rabbit between the formation of precipitin and the acceleration in the excretion of antitoxin (phase C of Glenny and Hopkins). They pointed out, however, that the results obtained in the rabbit may not be applicable to man, in whom precipitin formation following antitoxin administration is much less regular and less intense than in the rabbit. In fifteen patients injected with diphtherial antitoxin, they noticed no correlation between precipitin formation and the rapidity of serum excretion. Only one of the fifteen patients studied had ever received horse serum preceding this injection. In this case, the antitoxic curve in the blood stream was similar to those found in the other members of the series.

Similar conclusions were drawn by Schmid[138a] as a result of a more recent investigation of this subject. Five children were given injections of diphtherial antitoxin. After an interval of fourteen days the injections were repeated. Only severe local reactions developed after these reinjections. Titrations of antitoxic titer in the blood for forty days, starting with the initial injection, revealed similar curves after the first and second injections. The appearance of precipitins in three of these patients did not appear to influence the antitoxic curves.

An analysis of the evidence thus far reveals that the accelerated excretion of horse serum, which has been observed in sensitized rabbits, has not been clearly demonstrated in humans. The importance of the question warrants further investigation of the problem.

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Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL M. FEINBERG, M.D., AND THEODORE B. BERNSTEIN, M.D., CHICAGO

Asthma as a Sequel of Nasal Injury. Bourne, W. A.: Brit. M. J. 1: 870, 1939.

The author reports two cases in which asthma occurred several weeks after accidents in which severe nasal injury was accompanied by injuries of other parts of the body. A negative personal and family history of allergy was given by both patients. In one case an immediate nasal operation was followed by rapid relief and disappearance of the asthma. Operative repair was delayed in the second case, and relief did not occur until about a year after the septum resection.

Dermatitis, Urticaria and Aggravation of Nose Symptoms from the Oral Administration of Pollen Suspensions. Pollia, J. A.: California & West. Med. 50: 25, 1939.

Three cases are reported in which the administration of antigens in small dose by mouth caused unexpected reactions. In one patient, 5 drops of a 1:10,000 suspension of orris root resulted in dermatitis on two occasions. Another patient had two attacks of urticaria following the ingestion of 7 drops of 1:1,000 and 1 drop of 1:10,000 of pollen. A third individual, after taking 5 drops of a 1:10,000 suspension of pollen, had rhinitis, sneezing, and a dry cough.

Late Results of Treatment of Bronchial Asthma by Stellectomy. Leriche, R., and Fontaine, R.: Presse méd. 47: 243, 1939.

The authors report on the late results in eleven cases of stellectomy performed for the relief of bronchial asthma. The operation done was either a unilateral (left) or bilateral stellectomy. In six patients the results were good. One had complete cessation of symptoms without recurrence for 13 years, and another for 7½ years. A third patient had complete absence of symptoms for 7 years, followed by partial relapse. Three asthmatics had their conditions greatly improved, the improvement still persisting after periods of 4, 5½, and 2½ years, respectively. In five individuals lasting improvement failed to occur. The authors believe that stellectomy is the method of choice in the surgical treatment of asthma. The only likely neurologic complication is Bernard-Horner syndrome. They suggest that, as a temporary measure, infiltration of the stellate ganglion may be done. This may also serve as a means of estimating the probable result to be expected from stellectomy.

Ragweed Survey in Maine for 1938. Sylvester, C. B.: Maine M. J. 30: 97, 1939.

Another ragweed pollen survey of Maine was made by Sylvester in 1938. The results were practically a confirmation of those obtained in 1937. Aroostook County was again found practically free from ragweed, the count at Houlton being 57 for the entire season. Counts at other stations were also fairly low, the total counts for the season varying from 214 to 526.

Pollen Survey in Ames, Iowa, in 1938. Coles, J.: J. Iowa M. Soc. **28**: 198, 1939.

Coles made a pollen survey of Ames, Iowa (central portion of the state), during the 1938 season. For the grass season she reports the usual offenders (timothy, blue grass, orchard grass and redtop). The grass season begins the latter part of May and lasts until the middle of September. The height of the season occurs in early June, but a second peak occurs in August. In fact, the counts during August were as high as on many days during June and July. Ragweed is the most important pollen producer for the fall season. Although lamb's-quarter and pigweed grow profusely in the fall, they produce very little pollen. The author believes that hemp *(Cannabis sativa)* and Western water hemp *(Acnida tamariscina)*, on the basis of their distribution and pollen production, should be used more routinely in testing. Kochia (Mexican firebush) is also likely to be a cause of fall hay fever.

Coles has encountered large numbers of spores of *Alternaria, Hormodendrum,* rust, and smut on her slides throughout the summer and fall. It is her belief that these spores may play an important role in the causation of respiratory symptoms.

Dermatology

UNDER THE DIRECTION OF MARION SULZBERGER, M.D., NEW YORK, AND JOSEPH GOODMAN, M.D., BOSTON

Sensitivity to Silver Nitrate With an Eczematous Patch Test Reaction. Laugier, P., and Burgun, R.: Bull. Soc. franç. de dermat. et syph. **46**: 395, 1939.

A patient, 31 years of age, who presented an eczematous eruption on the face, was treated with 1 per cent and 2 per cent aqueous solutions of silver nitrate. When it was observed that new areas newly treated with silver nitrate solution soon showed vesiculation, the authors performed patch tests with the silver nitrate solution and with a colloidal silver preparation. After twenty-four hours there was a vesicular reaction to the silver nitrate but no reaction to the colloidal silver. In the discussion which follows the case report, both Woringer and Pautrier state that they have never seen hypersensitivity to silver nitrate and that they have never found vesicular patch test reactions to solutions of silver nitrate.

Four Attacks of Erythroderma From Bismuth. Glasser, M. R.: Bull. Soc. franç. de dermat. et syph. **46**: 398, 1939.

A patient with early syphilis developed a generalized erythroderma while under treatment with bismuth and an arsenical. After a slow recovery, he was treated with mercury for a period of a month, at the end of which time he was given one injection of a bismuth preparation. There was prompt recurrence of the erythroderma, less severe than the first attack. The patient was treated for several years thereafter with mercury only.

Seven years after first acquiring syphilis, the patient presented himself again with a dark-field positive chancre of the scrotum. One injection of a bismuth salt (not the same salt which had produced the previous attacks) resulted in a severe erythroderma. Four years later he was again given an injection of bismuth by mistake, with the same result.

The author points out that in this instance there was without doubt an allergic sensitivity to bismuth.

Dermatitis Due to a Sulphur-Meat Complex. Bernstein, J. C.: Arch. Dermat. & Syph. **40:** 414, 1939.

A grocer presented an eczematous eruption on the dorsal surfaces of the hands and wrists. Scratch, intracutaneous, and patch tests had been performed, with the discovery of a few slight reactions to substances with which the patient did not come in contact. It was discovered that the patient frequently handled meat which had been preserved in a sodium sulfite solution. Patch tests with a 1 per cent solution of sodium sulfite, with the liquid remaining after the preserving of the meat, and with fresh meat were uniformly negative. However, there was a positive patch test reaction to the preserved meat, appearing as erythema on the fourth day after application of the test and proceeding to vesiculation and pustulation. The author discusses the possibility that this patient was hypersensitive to a sulfurated protein or a colloidal sulfur-protein mixture. Strict avoidance of treated meat resulted in a complete disappearance of the eruption.

Clinical Characteristics and Pathogenesis of Pressure Urticaria. Gottron, H., and Lund, V.: Arch. f. Dermat. u. Syph. **179:** 308, 1939.

Pressure urticaria is not synonymous with dermographia. The term refers rather to the development of whealing at sites of pressure after a relatively long incubation period (1½ to 6 hours). An analysis of three cases (including one new one reported by the authors) reveals that, in two instances, urticaria of this type followed the administration of a barbiturate. In the authors' case there were also bullous lesions. In one attack these lesions were limited to areas exposed to light. It was then found that the urinary excretion of porphyrins by this patient was abnormally nigh.

The authors present the hypothesis that pressure urticaria is directly related to the porphyrins, the appearance of which, in their case, was secondary to the ingestion of a barbiturate.

Reactions in Tattoos. Madden, J. F.: Arch. Dermat. & Syph. **40:** 256, 1939.

Two kinds of reactions in tattoos are reported. In one instance there was swelling and itching in the red areas of a blue and red tattoo. Within twenty-four hours of tattooing the whole area was swollen and painful. After three weeks the reaction subsided in the blue areas, but the red areas had continued to be elevated and pruritic for seven years. Patch tests with various mercury compounds were positive, indicating allergic hypersensitivity to mercury.

The second patient reported on presented dark red elevated nodules in a tattoo which had been present for seven years before the appearance of the nodules. Histologic examination disclosed nests of epithelioid cells similar to those found in sarcoids. Patch tests with mercury and pigments were not performed in this instance.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., AND MAX HARTEN, M.D., BROOKLYN

The Histamine Content of the Blood of Guinea Pigs and Dogs During Anaphylactic Shock. Code, C. F.: Am. J. Physiol. **127:** 78, 1939.

The writers employed a modification of the Barsoun and Gaddum technique to study alterations in the histamine content of the blood during anaphylactic

shock in the guinea pig and the dog. Egg white and horse serum were used as sensitizing antigens.

During severe anaphylactic shock in guinea pigs, the histamine content of the blood increased from two to thirteen times the control value. Experiments in which lack of oxygen was induced by nitrogen administration revealed that the increased histamine content of the blood during severe anaphylactic reactions was not due to the coincident anoxemia.

In anaphylactic shock in dogs, the histamine content of the blood was increased from two to more than eighty times the control value. The maximal concentration was generally reached during the first ten minutes of the reaction. The histamine content then fell rapidly and frequently returned to normal within two or three hours. The rapid accumulation of histamine in the blood coincided with the fall of blood pressure. The pressure rose again when the histamine disappeared from the blood. At the time of the maximal concentration in the blood, from 79 per cent to 91 per cent of the blood histamine was found free in the plasma.

Since his observations on other species have given different results, the writer holds that the liberation of histamine during anaphylactic shock in the guinea pig and dog does not establish it as a fundamental accompaniment of anaphylaxis.

The Effects of Anaphylaxis and of Histamine Upon the Coronary Arteries in the Isolated Heart. Andrus, E. C., and Wilcox, H. B., Jr.: J. Exper. Med. **69**: 545, 1939.

In view of certain differences among various species in the reaction of the coronary arteries to histamine, the authors studied the anaphylactic reaction in the isolated heart of the cat, an animal in which histamine regularly brings about coronary dilatation.

Cats, sensitized to horse serum, were tested from four to ten weeks after the last sensitizing dose by the intravascular injection of 2 c.c. of serum. Four of five animals so tested survived prompt reactions characterized by rapid breathing, retching, vomiting, and defecation, followed by prostration.

The exposure of the isolated heart of the normal cat to horse serum results in a diminution of the coronary flow within fifteen seconds after the injection and a return to its previous state within thirty seconds. This reaction occurs in normal, sensitized, and desensitized hearts alike and tends to increase in intensity with successive injections. In the isolated hearts of sensitized cats, following the introduction of serum, the early evanescent coronary constriction is followed by a striking increase in coronary flow, beginning about one minute after the injection and lasting from two to five minutes. With subsequent exposures to the antigen the latter effect diminishes in intensity or fails to appear. These results are contrasted with those observed in the hearts of guinea pigs and rabbits, in which the coronary arteries are constricted during anaphylaxis. Attention is directed to the fact that, in the hearts of these three species, the effects of anaphylaxis and of histamine are qualitatively parallel.

The writers note that, among the effects of anaphylaxis upon smooth muscles in various organs, the effect upon the coronary arteries must also be considered.

The Effect of Volume of an Antigen Solution on Its Rate of Absorption. Bernstein, T. B., Rubin, S. S., and Feinberg, S. M.: J. Immunol. **36**: 309, 1939.

Subjects with negative cutaneous reactions to ragweed pollen were sensitized on the forearm with serial dilutions of a ragweed reagin-bearing serum, each dilution being half as strong as the preceding one. After twenty-four hours a "small

volume'' of ragweed in 0.2 c.c. of a 3 per cent solution was injected subcutaneously in the opposite arm. Forty-eight hours later the opposite forearm was sensitized, and the procedure was repeated, using an equivalent amount of antigen but in ''large volume,'' i.e., 2 c.c. of a 0.3 per cent solution. The time of appearance of the earliest and latest reactions at the sensitized sites and the highest dilution of reagin which reacted were measures of the rate and degree of absorption of the antigen. Control experiments were run in which the order of administration of the ''large'' and ''small volumes'' was reversed. In other cases the two administrations were separated by an interval of six days.

The average reaction time at the undiluted serum site was twenty-seven minutes with the ''small volume'' and forty-seven minutes with the ''large volume.'' In the majority of subjects the antigen appeared earlier in the circulation and reached a higher titer more rapidly with the ''small volume'' than with the ''large volume.'' From these findings the authors concluded that constitutional reactions are likely to occur more frequently and more rapidly with small concentrated doses of antigen than with the equivalent amounts in higher dilution.

With the same volumes of ragweed extract, absorption was shown to be more rapid with intracutaneous than with subcutaneous administration.

Serum-Sickness in Rabbits: VII. A Method for Removing or Destroying the Factor Causing Serum-Sickness. Fleisher, M. S., and Jones, L. R.: J. Immunol. **36**: 311, 1939.

The treatment of horse antisera of various types with heat and alkali over specified periods of time resulted in a destruction of the factor causing serum-sickness in rabbits. Destruction of the serum-sickness factor, however, was not obtained in every serum with the same technique. By varying the concentration of alkali, the temperature, the time of exposure to heat, and the dilution of the serum-alkali mixture, it was possible to destroy the factor causing serum-sickness without seriously impairing the antibody potency of the serum. The effect of the treatment upon the antibody potency varied in different sera containing the same type of antibody and in different types of antisera.

The results reported relate only to serum-sickness in the rabbit. Since some samples of treated serum proved toxic, the use of similarly treated serums in human beings is definitely contraindicated.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

Asthma in Children Treated With Autogenous Bronchoscopic Vaccine. Crump, J.: Am. J. Dis. Child. **58**: 768, 1939.

Two hundred and twenty-three consecutive children with asthma were bronchoscoped over a five-year period. Of these, there were 112 who were in regular attendance at the clinic for six months or more, and all received autogenous vaccine obtained by bronchoscopy. The latter procedure had revealed a purulent tracheobronchitis in 72 patients, and in 33, either early evidence of dilatation or definite bronchiectasis. In 2, the bronchi collapsed on inspiration. Only 4 children were found to have normal bronchi. It is emphasized that bronchial infection is far more frequent in asthmatic children than in asthmatic adults. It is also emphasized that the history in nearly every case was that the asthmatic attacks came on in relation to a ''cold.''

The vaccine treatment consisted in weekly subcutaneous injections of increasing doses, beginning with about 0.05 c.c. of a dilution in which from 100,000 to 500,000,000 organisms per cubic centimeter were present. A maximum dose of from 500,000,000 to 2,000,000,000 organisms was reached, and the quantity was then decreased and the interval lengthened.

Exact interpretation of results is difficult, for in only 27 patients were no other procedures carried out. Of these 27, complete relief was obtained in 23. Asthma developed within twelve hours of administration of vaccine in 11 cases.

Allergy of the Upper Respiratory Tract. Piness, G., and Miller, H.: J. A. M. A. **113**: 734, 1939.

Allergy is a nonsurgical disease of the nose and throat. In spite of this, in 43 per cent of a large group of asthmatic children, tonsillectomy had been done on the advice of a physician for the relief of asthma. Instead of accomplishing this result, it failed to do so, and in 17 per cent, seemed actually to aggravate or initiate the asthmatic state. One obvious cause of this unfortunate state of affairs is that allergic symptoms are mistaken for infectious ones, and the tonsils are thought to share in the infection. Lymphoid hyperplasia is one of the distinctive features of allergy, and enlarged tonsils are, therefore, characteristic, as is also regrowth of lymphoid tissue in the tonsillar fossa after tonsillectomy.

Apart from the question of allergy, there is much evidence to support the statement that many, if not most, of the 1,235,000 tonsillectomies a year in the United States in the age group under 15 years are unnecessary. The otolaryngologist, the pediatrician, and the general practitioner, in the order named, are held responsible for the unjustifiable lag in the application of our knowledge of allergy shown by this study.

Personality Factors in Neurodermite, A Case Study. Ackerman, N. W.: Psychosomatic Medicine **1**: 366, 1939.

This is a detailed analysis of the psychologic factors involved in an instance of neurodermite involving chiefly the arms, upper thorax, and neck. The patient was a half-orphan girl of 14 years, who had been reared in an institution and various foster homes. Initially the rash appeared at 2 years of age and was described as eczematoid and generalized. Scratch and patch tests were negative, whereas egg, wheat, and milk intradermally were strongly positive. Other intradermal tests were negative. Local, dietary, and other approaches to treatment, while improving the condition during hospitalization, failed to clear it entirely, and there was always an exacerbation after discharge from the hospital, sometimes immediately thereafter. The relationship of the patient's scratching to emotional disturbances, especially those of a sexual nature, is emphasized.

A Review of One Hundred and Twenty Cases of Bronchiectasis in Children in New South Wales. Selby, C.: M. J. Australia **2**: 352, 1939.

This is a report based on the study of 120 case records of bronchiectasis in children at the Royal Alexandra Hospital since 1918. While admitting that the etiology of bronchiectasis is unknown, the study indicates that pertussis plays an important etiological role. Allergy is likewise considered an important factor, although only a few proved instances of allergy in the group were brought to light. There were forty-seven instances of sinusitis.

The routine prophylaxis of pertussis by vaccine is suggested as one important means of reducing the incidence of bronchiectasis. Prognosis, without surgery, would seem to be good on the whole.

Note on Oral Administration of Potassium Chloride in the Treatment of Hay Fever, Nasal Allergy, Asthma, and Sinusitis. Abt, A.: Am. J. M. Sc. **198**: 222, 1939.

It is reported that the most striking results with oral potassium chloride were obtained in children who had both hay fever and asthma. The sinus tenderness and nasal fullness of several patients with sinusitis were also relieved. In instances of allergic rhinitis, the swelling and pallor of the nasal mucous membrane disappeared in three to five days, and discharge ceased. It is hypothicated that the action of potassium is to displace sodium in the tissues, thus producing a local tissue dehydration.

Twenty cases of children with allergic complaints who were improved by potassium chloride are listed. It is emphasized that it should not be given in capsule or tablet form, but only well diluted with water.

Importance of the Sensitization Mechanism in the Clinical Phenomenon of Allergy. Shaw, E. B., and Thelander, H. E.: Am. J. Dis. Child. **58**: 581, 1939.

The authors feel that study of the question of how sensitization occurs is of greater significance in solving the problem of allergy than is the study of avoiding reactions after it has occurred. They feel that the capacity to become sensitized is rather universal as allergic symptoms are so common; therefore, the constitutional factor cannot be the most important one. The search for some fairly simple and obvious factor would seem worth while and particularly suited to the infant group, where simplicity of diet and environment and absence of illness make for a problem attended by few variables. On looking for such a factor, vitamin C deficiency would seem to fit the bill, in the opinion of the authors. They list the evidence for this opinion, which includes Besredka's statement that guinea pig sensitization is more easily accomplished on a scurvy diet, the refractoriness of animals which synthesize their own vitamin C to sensitization, and the increased permeability of some tissues which might make for more intimate exposure to circulating antigens.

Additional evidence is the deficiency of vitamin C in the highly artificial human diet and the statement that humans alone, in the animal kingdom, develop spontaneous allergy. In the first few weeks of life and later at times of various sorts of nutritional disturbances, it seems that sensitization is especially apt to occur, and these are also times of low vitamin C intake.

Finally, since giving a routine ample daily dose of ascorbic acid, the authors have noted a considerable reduction in infantile colic, which they consider the only common allergic response of early infancy.

Rhinology and Ophthalmology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

Nasal Polypi and Edema. Mittermaier, R.: Ztschr. f. Hals-, Nasen- u. Ohrenh. **44**: 239, 1938.

Mittermaier reports further observations on the chemical aspects of nasal polyposis. He found that the protein content of the serum ranged between 0.5 per cent and 1.0 per cent, while the protein content of normal serum is about 7 per cent. This indicates that the polyp is not formed by the stasis of fluid. On the other hand, Mittermaier is of the opinion that it is probably caused by a greater permeability of the blood vessels. He suggests the following simple test

to determine the allergic response in cases of polyposis. Two-tenths of a cubic centimeter of physiologic saline is injected intracutaneously. A small wheal is found, followed by a secondary wheal. The secondary wheal disappears in about 6 to 12 minutes. In patients with hyperplastic states, who show a tendency to edema and polyposis, he found that usually the secondary wheal does not occur, and the primary wheal disappears in a much shorter time than 6 minutes. It is concluded that persons who show a rapid resorption of saline solution have a tendency toward polyposis, probably due to a certain degree of retention of salt in the skin. In treatment, he suggests a salt-free diet leaning toward the alkaline side of the acid-base ratio and a careful avoidance of any tendency to acidosis.

Nasal Allergy in Children. Barnett, E. J., and Carnahan, H. D.: Arch. Otolaryng. **30**: 247, 1939.

It is emphasized that allergy is a common cause of rhinitis in children, whether acute or chronic, seasonal or perennial, recurrent or constant, and that it is often unrecognized. A great deal of importance is placed upon the value of cytologic examinations of nasal secretions in diagnosis. Allergic control is vital if necessary associated surgical procedures are to be of benefit. Barnett and Carnahan point out that removal of infected tonsils and adenoids may aggravate symptoms in a child with uncontrolled allergy.

Nasal Sinusitis in Childhood. Crooks, J.: Brit. M. J. **1**: 935, 1938.

Crooks presents his observations on a series of 100 cases of sinusitis in children. In 24 patients the tonsils and adenoids were removed because of the presence of mucopus in the antrums. Further observations of these patients showed that after six months 16 still had the sinus condition. The following symptoms were most commonly listed: nasal or postnasal discharge, 84 cases; frequent colds, 83; cough, 82; mouth breathing, 62; headache, 44; and otitis media, 44. Diagnosis was made by transillumination, roentgenograms, and direct puncture. The predominating bacteria recovered from the sinuses were pneumococci and streptococci. When the antrum does not clear up after six irrigations, Crooks does an intranasal antrotomy. Of the 100 patients, 52 were cured, 32 improved, and 16 unchanged.

The majority of the papers which appear in the literature on sinus disease in children are of this type, in which allergy is not considered as an etiological factor. Even if an attempt were made to exclude cases of this type, it could not be done accurately without cytologic studies of the nasal and sinus secretions. It is probable that the group of cases reported by Crooks consisted of both allergic and infected or combined types.

Pathologic Nasal Conditions Affecting Clinical Allergy. Agar, J. S., and Cazort, A.: South. M. J. **32**: 1063, 1939.

In a study of the relationship of nasal allergy and other manifestations, Agar and Cazort conclude by emphasizing the following points: (1) Studies of the nasal and bronchial secretions give the only reliable means of diagnosing infected and infectious asthma; (2) a submucous resection properly done is of great benefit in a large percentage of cases of hay fever and asthma; and (3) in sinus disease conservative surgery is preferable, and it offers good results in inverse ratio to the duration and severity of the asthma.

Attacks of Ménière's Disease and Attacks of Iritis Together With Angioneurotic Edema of the Lids in the Same Patient. Granström, K. O., and Nylen, C. O.: Acta. oto-laryng. 26: 717, 1939.

The patient, a woman aged 56 years, had had for several years repeated attacks of Ménière's disease and also of palpebral edema of the angioneurotic type, accompanied by iritis-like attacks of short duration. This latter was considered as "an intraocular edema of Quincke," and the attacks of Ménière's disease were thought to be an analogous process in the labyrinth. All the symptoms were considered allergic in nature, although the offending allergen was not found. The examination of the function of the labyrinth and cochlea showed normal findings between attacks. During the Ménière attacks, vertigo, rotary-horizontal nystagmus on change of position of the head, and a marked reduction of hearing in the left ear developed.

Miscellaneous

Allergic (?) Symptoms in Cases of Kala-Azar Treated With Antimony Salts. Dasgupta, N. C.: J. Indiana M. A. 8: 237, 1939.

Two patients with kala azar were treated with urea stibamine (antimony) injected intravenously every fourth day. In the first patient no effect was noted with the initial small doses (0.02 to 0.05 gm.). The fourth dose of 0.07 gm. was followed in two minutes by a rapidly spreading intense urticarial eruption, with swelling of the lips and tongue, dyspnea, cyanosis, and loss of consciousness. Very shortly after the subcutaneous injection of adrenalin (1 c.c.) the eruption subsided, but prostration persisted several hours. Six days later 0.05 gm. of the drug, given intravenously, was followed immediately by burning sensation all over the skin; this was controlled by adrenalin. A subsequent injection of 0.025 gm. caused no symptoms.

The second patient, given 0.005 gm. of urea stibamine intravenously at once, began to vomit and a generalized urticarial rash appeared. These symptoms were promptly relieved by adrenalin.

The author comments on the fact that those reactions were frequent and death was not altogether rare in the early days of urea stibamine treatment when large doses were used. Since employment of much reduced quantities, these presumably allergic symptoms have become very rare.

Studies in Mucous Membrane Hypersensitivities. III. Allergic Reaction of Passively Sensitized Rectal Mucous Membrane. Gray, I., and Walzer, N.: Am. J. Digest. Dis. 4: 707, 1938.

The authors have shown that the mucous membrane of the rectum can be sensitized passively with human serum containing reagens. The serum is injected into the rectum mucous membrane 2 to 6 cm. from the anus, and the skin of the forearm was injected as a control. Peanut was the allergin. This, when taken by mouth or instilled rectally, induced a reaction characterized by edema, hyperemia, and increased mucous secretions. Symptomatically, there was pruritus, burning, a sense of fullness, and a desire to empty the bowel.

Correspondence

The Editor,
THE JOURNAL OF ALLERGY.

Owing to my geographical location, especially during the winter months, other allergy workers have fairly frequently referred patients to me for continuance of routine injections during a temporary stay here. The patients bring material and ordered dosages.

Occasionally unforeseen delays produce unexpectedly long intervals between treatments. At times the preceding dose given elsewhere has caused a large local reaction, and I am faced with the problem of administering a dose from a bottle upon which the strength and occasionally the composition of its contents may not be stated. This invites the possibilities of overdosage with constitutional reactions or the ruining of previous excellent results by strict adherence to the schedule of doses presented.

My suggestion is that each bottle be clearly labeled concerning its contents and strength. Moreover, the patient should be given a letter stating a general idea of his type, his sensitivity, whether high or ordinary, his proneness to constitutional reactions, and his ability to tolerate moderate local reactions.

I feel certain that I am voicing the sentiments of those practicing allergy on what might be termed the "tourist trail."

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October 20, 1939